07/236724

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PATENT
ATTORNEY DOCKET NO.: 061635-0007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,937,078
Granted: June 26, 1990

Patentees: Michael MEZEI and Adrienn GESZTES

Assignee: Mezei Associates Limited

FOR: LIPOSOMAL LOCAL ANESTHETIC AND ANALGESIC

Commissioner for Patents
U.S. Patent and Trademark Office
220 20th Street S.
Customer Window, **Mail Stop Patent Ext.**
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Date: July 7, 2004

FEE COVER SHEET FOR
REQUEST FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

1. Transmitted herewith is a REQUEST FOR EXTENSION OF PATENT TERM PURSUANT TO 35 U.S.C. § 156 including Exhibits 1-7 (Original + 4 sets).

2. Constructive Petition

☒ EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

3. Fee Calculation (37 C.F.R. §1.16)

Fee for Patent Term Extension	$ 1,120.00
Reduction by ½ for filing by a small entity	$ 0.00
TOTAL FEE =	$ 1,120.00

4. Fee Payment

☒ The Commissioner is hereby authorized to charge $1,120.00 to Deposit Account No. 50-0310 for Extension of Term of Patent (37 C.F.R. §1.20(j)(1) (PTO Fee Code 111).

☒ The Commissioner is hereby authorized to charge any additional fees which may be required, including fees due under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account 50-0310.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: July 7, 2004

By: _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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REQUEST FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

Applicant, Mezei Associates, Ltd. ("Mezei"), a corporation created and existing under the Laws of Canada, represents that it is the owner of the entire interest in and to United States Patent No. 4,937,078 for LIPOSOMAL LOCAL ANESTHETIC AND ANALGESIC PRODUCTS granted to Michael MEZEI and Adrienn GESZTES on June 26, 1990 by virtue of an assignment from Michael MEZEI to Mezei, recorded at frame 005044, reel 0743, and an assignment from Adrienn GESZTES to Mezei, recorded at frame 005044, reel 0741. A copy of the assignments are attached hereto as **Exhibit 1**. A Grant of Power of Attorney, authorizing the registered practitioners of Morgan, Lewis & Bockius LLP to act of behalf of Mezei for the purposes of obtaining a patent term

extension for United States patent no. 4,937,078, with correspondence and communications to be directed as set forth therein and in section (15) of this Application, is being filed concurrently herewith. A copy of the Grant of Power of Attorney is attached hereto as **Exhibit 2**.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 *et seq.*, and follows the numerical sequence and format as set forth in 37 C.F.R. § 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is SURPASS®, which is further identified as follows:

Chemical Name:

sodium [o-(2,6-dichloroanilino)phenyl]acetate, as set forth in the approved label insert.

Generic Name:

Diclofenac sodium

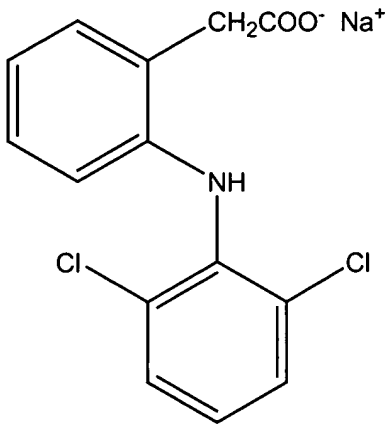
Molecular Formula:

$C_{14}H_{10}Cl_2NNaO_2$

Molecular Weight:

318.13

Structural Formula:



Diclofenac sodium, as described above, is the active ingredient of the approved product, SURPASS®, as can be seen from the approved labeling for SURPASS®. A copy of the approved labeling for SURPASS® is attached hereto as **Exhibit 3**.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

SURPASS® was subject to regulatory review under Section 512(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §360(b)).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

SURPASS® received permission for commercial marketing or use under Section 512(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §360(b)) upon approval of NADA 141-186 on May 13, 2004.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or

use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient of SURPASS® is diclofenac sodium. Diclofenac sodium has been approved for commercial marketing and use in humans under section 505(b) of the Federal Food, Drug and Cosmetic Act. Diclofenac sodium, has not been approved for commercial marketing and use in animals under section 512(b) of the Federal Food, Drug and Cosmetic Act prior to approval of NADA 141-186 on May 13, 2004.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

SURPASS® was approved on May 13, 2004, and the last day within the sixty day period permitted for submission of an application for patent term extension is July 13, 2003. Accordingly, this application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f).

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

The complete identification of the patent for which an extension is being sought is as follows:

Inventor:	Michael MEZEI and Adrienn GESZTES
U.S. Patent No.:	4,937,078
Issue Date:	June 26, 1990
Expiration Date:	August 26, 2008

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A full copy of U.S. Patent No. 4,937,078, for which extension is being sought, is attached hereto as **Exhibit 4**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

A copy of the maintenance fee statement showing timely payment of each maintenance fee when due is attached as **Exhibit 5**.

No disclaimer, certificate of correction, or reexamination certificate has been filed and/or issued for U.S. Patent No. 4,937,078.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product.

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

Claim 14 of U.S. Patent 4,937,078 reads on the method of using the approved product, as detailed below.

Claim 14 of U.S. Patent 4,937,078 reads as follows:

> 14. A method for providing local anesthesia or analgesia to a mammal which comprises topically applying to said mammal a composition containing phospholipid vesicles encapsulating 0.1 to 10% by wt. of an anesthetic or analgesic agent, wherein said composition is applied in an amount between about 0.005 to 0.5 g/cm^2 of surface to be anesthesized.

As set forth on page 1 of the labeling for the approved product, **Exhibit 3**, SURPASS® is indicated for control of pain and inflammation associated with osteoarthritis in the joints of horses by applying a 5" ribbon of SURPASS® topical cream twice daily over the affected joint. As also set forth on page 1 of the labeling, SURPASS® is a topical cream containing 1% diclofenac sodium in a base composed of Phospholipoin 90H (a phospholipid), propylene glycol, alcohol, vitamin E acetate,

benzethonium chloride, and purified water in a liposomal formulation, *i.e.*, a phospholipid vesicles. As set forth on page 2 of the labeling, SURPASS® is a non-steroidal anti-inflammatory drug with analgesic properties, *i.e.*, an analgesic agent. Applying a 5" ribbon of SURPASS® to the joint of a horse corresponds to applying the composition in an amount between about 0.005 to 0.5 g/cm^2. For example, the surface area of the knee joint of a horse is about 730 cm^2 and a 5" ribbon of SURPASS® corresponds to about 7.3 g of SURPASS® (this is because a 5" ribbon of SURPASS® contains about 73 mg of diclofenac sodium at a concentration of about 1% (*See*, package insert page 2, section on effectiveness))[1]. Therefore, applying a 5" ribbon of SURPASS® to the knee joint of a horse corresponds to applying the composition in an amount of about 0.01 g/cm^2 (7.3g / 730 cm^2). The largest joint of a horse for which SURPASS® is intended to be applied is the hock, which has a surface area about 1.5 times larger than the surface area of the knee. Accordingly, applying SURPASS® to the hock of a horse corresponds to applying the composition in an amount of about 0.007 g/cm^2. The smallest joint of a horse for which SURPASS® is intended to be applied is the interphalangeal joint, which has a surface area about 0.5 times smaller than the surface area of the knee. Accordingly, applying SURPASS® to the interphalangeal joint of a horse corresponds to applying the composition in an amount of about 0.02 g/cm^2. Or, considered another way, applying 7.3 g of SURPASS® in an amount between about 0.005 to 0.5 g/cm^2 corresponds to covering a surface of an area between about 14.6 cm^2 and 1,460 cm^2. The area of the joints of a horse for which SURPASS® is intended to be applied all fall within this range. Therefore, claim 14 reads on a method of using the approved product.

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[1] The area of the knee joint of a horse can be estimated by approximating that the knee joint is a cylinder 15.24 cm (6 inches) high and 15.25 cm (6 inches) in diameter and using the formula for the area of the sides of a cylinder (area of sides of a cylinder = circumference x height, wherein circumference is π x diameter) to calculate the area of the knee joint.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(ii) For a patent claiming a new animal drug:

(A) The date a major health or environmental effects test on the drug was initiated, and any available substantiation of that date, or the date of an exemption under subsection (j) of section 512 of the Federal Food Drug and Cosmetic Act became effective for such animal drug;

On January 11, 1999 the FDA granted IDEXX's request for a categorical exclusion from preparing an environmental assessment. A copy of the FDA letter granting the request for categorical exclusion is attached hereto as **Exhibit 6**. This establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(4) as January 11, 1999.

(B) The date on which a new animal drug application (NADA) was initially submitted and the NADA number; and

The initial submission constituting NADA 141-186 for SURPASS® was on December 27, 2000 (**Exhibit 7**). The FDA acknowledged receipt of the initial submission and assigned the submission NADA number 141-186 on January 2, 2001 (**Exhibit 8**). This establishes the "initial" submission date of NADA 141-186 under 35 U.S.C. 156(g)(4) as January 2, 2001.[2]

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[2] This is consistent with FDA's policy, as stated in FDA's proposal to amend 21 C.F.R. § 60.1, Patent Term Restoration Regulations, that the date "a NADA will be considered to have been initially submitted with respect to the animal drug product under section 512(b) of the act will be the date of FDA's official acknowledgement letter assigning a number to the NADA" (*See*, FDA's proposal to amend 21 C.F.R. § 60.1, Patent Term Restoration Regulations, 56 Fed. Reg. 5784, February 13, 1991, (**Exhibit 9**)).

(C) The date on which the NADA was approved.

The NADA was approved by the FDA in an approval letter sent May 13, 2004. A copy of this FDA approval letter is attached as **Exhibit 10.** This establishes the end of the "regulatory review period" under 35 U.S.C. 156(g)(4) as May 13, 2004.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The regulatory activities undertaken to obtain approval of SURPASS® commenced with the submission of an Investigational New Animal Drug (INAD) Application by Blue Ridge Pharmaceuticals, Inc. ("Blue Ridge", now IDEXX Pharmaceuticals, Inc. ("IDEXX")) on March 6, 1998 to study the use of 1% topical diclofenac in a liposomal base for the relief of pain and inflammation in horses. On March 11, 1998, the FDA acknowledged receipt of the INAD application and assigned the submission INAD number 10-294.

Although, Mezei, the applicant for this patent term extension, did not undertake activities for marketing approval before the FDA, Mezei is authorized to rely upon the activities of Blue Ridge before the FDA as evidenced by a letter from IDEXX specifically authorizing such reliance. A copy of the letter from IDEXX is attached hereto as **Exhibit 11**.

A developmental conference with the FDA was requested on June 30, 1998 and a developmental conference was held on August 14, 1998. Minutes of the developmental conference were provided by the FDA on August 17, 1998.

Protocols for the clinical study and target animal safety studies were submitted on September 8, 1998 and the FDA completed review of the clinical study and target animal safety studies on January 11, 1999. On January 11, 1999 the FDA also granted Blue Ridge's request for categorical exclusion from the requirement to prepare an environmental assessment.

Pivotal clinical studies began in December 16, 1998 and ended on April 15, 1999. Clinical studies were initiated prior to receiving the January 11, 1999 letter from the FDA, providing the FDA's review of the clinical study and target animal safety studies, since the FDA provided their comments to Blue Ridge in an earlier teleconference.

The Chemistry Manufacturing and Controls section was submitted to the FDA on April 30, 1999.

A teleconference was held with the FDA on May 11, 1999 to discuss the statistical methodology for the pivotal clinical study.

The Clinical Efficacy section was submitted to the FDA on October 1, 1999.

The Proposed Labeling section was submitted to the FDA on October 1, 1999.

The Target Animal Safety section was submitted to the FDA on November 23, 1999.

On January 21, 2000, the FDA provided comments on the Clinical Efficacy section.

On February 11, 2000, the FDA provided comments on the Chemistry Manufacturing and Controls section.

On March 23, 2000 Blue Ridge requested a teleconference to discuss the Clinical Efficacy section. The teleconference took place on May 2, 2000 and the FDA provided minutes from the teleconference on June 12, 2000.

On June 14, 2000, the FDA provided comments on the Proposed Labeling section.

On August 31, 2000, the FDA provided comments on the Target Animal Safety section.

On December 27, 2000, IDEXX submitted a complete NADA that addressed all of the comments provided by the FDA. On January 2, 2001, the FDA assigned the NADA number 141-186.

IDEXX filed amendments to NADA 141-186 on February 19, 2001; October 3, 2001; October 4, 2001; and December 14, 2001.

On February 26, 2002, the FDA mailed a letter indicating that NADA 141-186 was incomplete.

On February 27, 2002, IDEXX had a teleconference with the FDA to discuss the labeling. Minutes from the teleconference were provided by FDA on March 26, 2002. On April 16, 2002, IDEXX had a second teleconference with the FDA to discuss labeling. Minutes from the second teleconference were provided by the FDA on May 13, 2002.

IDEXX re-submitted NADA 141-186 on May 31, 2002.

IDEXX filed amendments to NADA 141-186 on August 28, 2002 and October 11, 2002.

On June 6, 2003, the FDA mailed a letter indicating that NADA 141-186 was incomplete.

IDEXX re-submitted NADA 141-186 on August 26, 2003.

IDEXX filed amendments to NADA 141-186 on December 2, 2003; February 23, 2004; February 24, 2004; March 3, 1004; and March 19, 2004.

NADA 141-186 was approved by the FDA on May 13, 2004.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Statement That The Patent Is Eligible For Extension:

Applicant is of the opinion that U.S. Patent 4,937,078 is eligible for extension under 35 U.S.C. 156(a) because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C. 156(a)

U.S. Patent 4,937,078 claims a method of using the approved product, as detailed in section (9) above.

(2) 35 U.S.C. 156(a)(1)

U.S Patent 4,937,078 granted on June 26, 1990 from U.S. application no. 07/236,724, filed on August 26, 1988. Accordingly, the expiration date of the patent is August 26, 2008.[3] This application, therefore, has been submitted before the expiration of the patent term.

(3) 35 U.S.C. 156(a)(2)

The term of this patent has never been extended.

(4) 35 U.S.C. 156(a)(3)

This application is submitted by the owner of record in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office. Mezei is the owner of record of the patent by virtue of an assignment from inventor Michael MEZEI to Mezei, recorded at frame 005044, reel 0743, and an assignment from inventor Adrienn GESZTES to Mezei, recorded at

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[3] The term of a patent in force on June 8, 1995 is the greater of the date that is 20 years from the date on which the application was filed, if the application does not claim priority to any earlier filed application, or 17 years from the patent grant. 35 U.S.C. § 154(c) and MPEP 2701. Accordingly, the expiration date of U.S. Patent 4,937,078 is August 26, 2008, *i.e.*, 20 years from the date on which the application was filed.

frame 005044, reel 0741. Copies of these assignments are attached hereto as **Exhibit 1**.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the May 13, 2004 approval letter from the FDA (**Exhibit 10**), SURPASS® was subject to a regulatory review period under Section 512(b) of the Federal Food, Drug, and Cosmetic Act before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)(i)

The permission for commercial marketing of SURPASS® after this regulatory review period is the first permitted commercial marketing of SURPASS® under a provision of the Federal Food, Drug and Cosmetic Act (Section 512(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §360(b)) under which the regulatory review period occurred, as confirmed by the absence of any approved NADA for the approved product prior to May 13, 2004.

(7) 35 U.S.C. 156(c)(4)

No other patent has been extended for the same regulatory review period for the product SURPASS®.

Statement as to Length of Extension Claimed:

The term of U.S. Patent No. 4,937,078 should be extended by **1590** days, from August 26, 2008 to January 3, 2013. This extension is calculated on the following basis:

Title 35 U.S.C. 156(c) provides that the term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued, except that -- (1) each period of the regulatory review period shall be reduced by any period during which the applicant for the patent extension did not act with due diligence; (2)

after any such reduction required by paragraph (1), the period of extension shall include only one-half of the time remaining in the period under section 156(g)(4)(B)(i) (the earlier of the date a major health or environmental effects test on the drug was initiated or the date an exemption under subsection (j) of section 512 became effective for the new animal drug product); and (3) the total of the period of extension plus the period remaining in the term of the patent after the date of approval shall not exceed fourteen years. The "regulatory review period" is defined in section 156(g)(4), for a new animal drug product, as being the sum of (i) the earlier of the date a major health or environmental effects test on the drug was initiated or the date an exemption under subsection (j) of section 512 became effective for the approved new animal drug product and ending on the date an application was initially submitted for such animal product under section 512, and (ii) the period beginning on the date the application was submitted for the approved animal drug product under section (b) of section 512 and ending on the date such application was approved under such section. Section 156(g)(6) further provides that if the patent involved was issued after the date of the enactment of this section (September 24, 1984), then the period of extension may not exceed five years.

In context of the implementing regulations of 37 C.F.R. 1.778 with respect to patent term extensions for an animal drug product, the term extension of U.S. Patent No. 4,937,078 based on the regulatory review for SURPASS® was determined as follows:

> **Sec. 1.778 Calculation of patent term extension for an animal drug product.**
> **(a) If a determination is made pursuant to Sec. 1.750 that a patent for an animal drug is eligible for extension, the term shall be extended by the time as calculated in days in the manner indicated by this section. The patent term extension will run from the original expiration date of the patent or any earlier date set by terminal disclaimer (§ 1.321).**

U.S. Patent No. 4,937,078 was issued on June 26, 1990 from U.S. application no. 07/236,724, filed on August 26, 1988. Pursuant to 35 U.S.C. 154(c), this patent is entitled to an original term of 20 years from August 26, 1988, which provides an original expiration date of August 26, 2008.

(b) The term of the patent for an animal drug will be extended by the length of the regulatory review period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.

(c) The length of the regulatory review period for an animal drug will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(4)(B), it is the sum of--

(1) The number of days in the period beginning on the earlier date a major health or environmental effects test on the drug was initiated or the date an exemption under subsection (j) of section 512 became effective for the approved animal drug product and ending on the date an application was initially submitted for such animal drug under section 512 of the Federal Food, Drug, and Cosmetic Act; and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved animal drug under subsection (b) of section 512 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days in the period beginning on the earlier date a major health or environmental effects test on the drug was initiated or the date an exemption under subsection (j) of section 512 became effective for the approved animal drug product and ending on the date an application was initially submitted for such animal drug under section 512 of the Federal Food, Drug, and Cosmetic Act, *i.e.,* the period defined under 37 C.F.R. § 1.778(c)(1), extends from January 11, 1999 (the date an exemption under subsection (j) of section 512 became effective for the approved animal drug product (**Exhibit 6**)) to January 2, 2001 (the date an application was initially submitted for such animal drug under section 512 of the Federal Food, Drug, and Cosmetic Act, (**Exhibit 8**)) and is **723** days.

The number of days in the period beginning on the date the application was initially submitted for the approved animal drug under subsection (b) of section 512 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section, *i.e.,* the period defined under 37 C.F.R. § 1.778(c)(2), extends from January 2, 2001 (the date application was initially submitted for the approved animal drug under subsection (b) of section 512 of the Federal Food, Drug, and

Cosmetic Act (**Exhibit 8**)) to May 13, 2004 (the date such application was approved under such section (**Exhibit 10**)) and is **1228** days.[4]

The regulatory review period is the sum of the periods of defined under 37 C.F.R. § 1.778(c)(1),and (c)(2) and is **1951** days.

> **(d) The term of the patent as extended for an animal drug will be determined by--**
> **(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:**
> **(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;**
> **(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;**
> **(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) of this section; half days will be ignored for purposes of subtraction;**

With respect to 37 C.F.R. § 1.778 (d)(1)(i), **0** days of the periods defined in paragraphs (c)(1) and (c)(2) were before the June 26, 1990 date on which U.S. Patent 4,937,078 issued.

With respect to paragraph 37 C.F.R. § 1.778(d)(1)(ii), there were **0** days during which applicant did not act with due diligence during the periods defined in 37 C.F.R. § 1.778 (c)(1) and (c)(2), as detailed in section (11) above.

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[4] We note that the approval letter for NADA (**Exhibit 10**) suggests that NADA 141-186 was initially submitted on August 26, 2003. It is our understanding, however, that the FDA considers the date an NADA is initially submitted to be "the date of FDA's official acknowledgement letter assigning a number to the NADA" (*See*, FDA's proposal to amend 21 C.F.R. § 60.1, Patent Term Restoration Regulations, 56 Fed. Reg. 5784, February 13, 1991, (**Exhibit 9**)). Accordingly, the August 26, 2003 appears to be the incorrect designation of the filing date for the purposes of determining the patent term extension. Applicant's of this Request for Patent Term Extension consider January 2, 2001 (the date application was initially submitted for the approved animal drug under subsection (b) of section 512 of the Federal Food, Drug, and Cosmetic Act, *i.e.*, "the date of FDA's official acknowledgement letter assigning a number to the NADA" (**Exhibit 8**)) to be the filing date for the purposes of determining the patent term extension.

With respect to 37 C.F.R. § 1.778 (d)(1)(iii), one-half of the number of days remaining in the period defined by paragraph 37 C.F.R. § 1.778(c)(1) after that period is reduced in accordance with 37 C.F.R. § 1.778(d)(1) (i) and (ii) is one-half of **723** days days, which is **361** days.

Subtracting from the regulatory review period of **1951** days as determined above pursuant to 37 C.F.R. § 1.775(c) the number of days determined above with respect to 37 C.F.R. § 1.778(d)(1)(i), (ii), and (iii), the term of patent extension is **1951** days minus **0** days, minus **0** days, minus **361** days, for a sum total of **1590** days.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The original term of U.S. Patent No. 4,937,078 is August 26, 2008 and is not shortened by terminal disclaimer. Adding the **1590** days as determined in 37 C.F.R. § 1.778(d)(1) to the original term of the patent results in an extended term to January 3, 2013.

(3) By adding 14 years to the date of approval of the application under section 512 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to the May 13, 2004 date of the approval of the NADA results in a date **May 13, 2018**.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier of January 3, 2013 and May 13, 2018 is January 3, 2013.

(5) If the original patent was issued after November 16, 1988, by--,
(i) adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and
(ii) comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

U.S. Patent No. 4,937,078 issued after November 16, 1988. Adding 5 years to the original expiration date of the patent (there was no terminal disclaimer) of August 26, 2008 gives a date of August 26, 2013. The earlier of January 3, 2013 and August 26, 2013 is January 3, 2013.

(6) If the original patent was issued before November 16, 1988, and
(i) If no major environmental effects test on the drug was initiated and no request was submitted for an exemption under subsection (j) of section 512 of the Federal Food, Drug, and Cosmetic Act before November 16, 1988, by--
(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and
(B) Comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) of this section with each other and selecting the earlier date; or
(ii) If a major environmental effects test on the drug was initiated and no request was submitted for an exemption under subsection (j) of section 512 of the Federal Food, Drug, and Cosmetic Act before November 16, 1988, and the application for commercial marketing or use of the animal drug was not approved before November 16, 1988, by--
(A) Adding 3 years to the original expiration date of the patent or earlier date set by terminal disclaimer, and
(B) Comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(ii)(A) of this section with each other and selecting the earlier date.

U.S. Patent No. 4,937,078 issued after November 16, 1988. Accordingly, this section is not applicable to determining the patent term extension.

Thus, as calculated above, the term of U.S. Patent No. 5,770,599 is eligible for a **1590** day extension until January 3, 2013.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765).

Applicant acknowledges a duty to disclose to the Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j)).

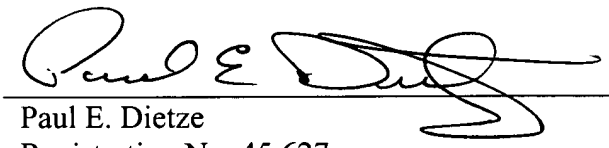
As noted in the letter of transmittal submitted with this application, the Patent and Trademark Office is authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or to credit any overpayment to Deposit Account No. 50-0310.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

In accordance with the Grant of Power of Attorney, filed concurrently herewith, authorizing the registered practitioners of Morgan, Lewis & Bockius LLP to act of behalf of Mezei for the purposes of obtaining a patent term extension for United States patent no. 4,937,078 (copy attached as **Exhibit 2**), please address all inquiries and correspondence relating to this application for patent term extension to:

Paul E. Dietze
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Telephone: 202-739-5667
Facsimile: 202-739-3001

Respectfully Submitted,
Morgan, Lewis & Bockius LLP

Date: July 7, 2004 By: 

Morgan Lewis & Bockius LLP
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Tel. No.: 202-739-3000

Paul E. Dietze
Registration No. 45,627
Tel. No.: (202) 739-5667
Fax No.: (202) 739-3001

Exhibit 1

A 1185223

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 22, 2004

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON October 18, 1988

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. Jackson

H. L. JACKSON
Certifying Officer

ASSIGNMENT

WHEREAS, I, MICHAEL MEZEI, a citizen of Canada, residing at 14 Starling Street, Nova Scotia, Canada B3M 1V8, have jointly invented with ADRIENN GESZTES certain new and useful improvements in LIPOSOMAL LOCAL ANESTHETIC AND ANALGESIC PRODUCTS for which an application for Letters Patent of the United States was executed on even date herewith; which application was filed in the United States Patent and Trademark Office on August 26, 1988 and accorded Serial No. 236,724; and

WHEREAS, MEZEI ASSOCIATES LIMITED, a corporation duly organized under the laws of Canada, having a place of business in Nova Scotia, Canada, is desirous of acquiring the entire right, title and interest in and to the aforesaid invention and in and to any Letters Patent of the United States or any foreign country which may be granted therefor;

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) and other good and valuable consideration, the receipt of which is hereby acknowledged, I, the said MICHAEL MEZEI by these presents do sell, assign, and transfer unto MEZEI ASSOCIATES LIMITED, its successors, legal representatives and assigns, the full and exclusive right to the said invention as described in the said application, and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations and extensions thereof;

AND I HEREBY authorize and request the Commissioner of Patents and Trademarks or any other proper officer or agency of any country to issue all said Letters Patent to said assignee;

AND I HEREBY warrant and covenant that I have full right to convey the entire interest herein assigned and that I have not

executed and will not execute any instrument or assignment in conflict herewith;

AND I HEREBY agree to communicate to said assignee or its representatives any facts known to me respecting said invention, to execute all divisional, continuation, reissue and foreign applications, sign all lawful documents and make all rightful oaths relating to said invention, and to testify in any judicial or administrative proceeding and generally do everything possible to aid the said assignee to obtain and enforce said Letters Patent in the United States or any foreign country when requested so to do by said assignee.

IN WITNESS WHEREOF, I have hereunto set my hand and seal.

Sept 29 1988
(Date)

Michael Mezei
Michael Mezei

REEL 5044 FRAME 742

On this 29 day of September, 1988, before me a Notary Public, personally appeared MICHAEL MEZEI, to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and acknowledged the same to be his free act and deed.

RECEIVED
OCT 18 88

(SEAL)

JOSEPH W. PETTIGREW Notary Public
A Barrister of the Supreme Court of Nova Scotia
My Commission Expires:

no expiry date.

A 1184838

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 21, 2004

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON OCTOBER 18, 1988.

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. K. HAWKINS
Certifying Officer

ASSIGNMENT

WHEREAS I, ADRIENN GESZTES, a citizen of Hungary, have jointly invented with MICHAEL MEZEI, a citizen of Canada, residing at 14 Starling Street, Nova Scotia, Canada, B3M 1V8, certain new and useful improvements in LIPOSOMAL LOCAL ANESTHETIC AND ANALGESIC PRODUCTS, for which an application for Letters Patent of the United States will be filed in the United States Patent and Trademark Office.

WHEREAS, MEZEI ASSOCIATES LIMITED, a corporation duly organized under the laws of the Canada, having a place of business in Nova Scotia, Canada, is desirous of acquiring the entire right, title and interest in and to the aforesaid invention as described and set forth in Exhibit "A" annexed hereto to this Assignment and in and to any Letters Patent of the United States or any foreign country which may be granted therefor;

NOW THEREFORE, in consideration of the sum of One Dollar ($1.00) and other good and valuable consideration, the receipt of which is hereby acknowledged, I the said ADRIENN GESZTES by these presents do sell, assign, and transfer unto MEZEI ASSOCIATES LIMITED, its successors, legal representatives and assigns, the full and exclusive right to the said invention as described in the said Exhibit "A" annexed hereto and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations and extensions thereof;

AND I HEREBY authorize and request the Commissioner of Patents and Trademarks or any other proper officer or agency of any country to issue all said Letters Patent to said assignee;

AND I HEREBY warrant and covenant that I have full right to convey the entire interest herein assigned and that I have not executed and will not execute any instrument or assignment in conflict herewith;

AND I HEREBY agree to communicate to said assignee or its representatives any facts known to me respecting said invention, to execute all divisional, continuation, reissue and foreign applications, sign all lawful documents and make all rightful oaths relating to said invention, and to testify in any judicial or administrative proceeding and generally do everything possible to aid the said assignee to obtain and enforce said Letters Patent in the United States or any foreign country when requested so to do by said assignee.

IN WITNESS WHEREOF, I have hereunto set my hand and seal.

[illegible])
City of [illegible]) ss
[illegible])
States of America)

AUGUST 24, 1988
(Date)

Gesztes Adrienn
Adrienn Gesztes

On this 24th day of AUGUST, 1988, before me a Notary Public, personally appeared Adrienn Gesztes, to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and acknowledged the same to be their free act and deed.

(SEAL)

Elizabeth Barnett
~~Notary Public~~

Elizabeth Barnett
Consul of the United States
of America

"Schedule A"

PATENT APPLICATION

Title: THE USE OF LIPOSOMES TO ENHANCE LOCAL ANESTHETIC EFFECT

Inventor: Michael Mezei and Adrienn Gesztes, Halifax, Canada

Assignee: Mezei Associates Ltd., Halifax, N.S. Canada

ABSTRACT

Liposome encapsulated local anesthetic agents when applied to skin or mucous membranes provide greater local anesthesia and analgesia than the same agents incorporated in conventional vehicles i.e., ointment, cream or lotion.

BACKGROUND OF THE INVENTION

Liposomes - vesicles consisting of phospholipid membranes - have been studied in recent years to utilize them for altering the pharmacokinetic properties of drugs encapsulated into them. A few studies focused on their potential as drug carriers in topical preparations, involving corticosteroids, econazole, progesterone and methotrexate. Liposomal formulations delivered

more of these drugs into the skin than conventional vehicles, and also localized them at the desired site of action (M. Mezei in "Liposomes as Drug Carriers" ed. G. Gregoriadis, John Wiley & Sons Ltd. New York 1988 page 663-677).

Topical anesthetics are agents that reversibly block nerve conduction causing numbness and cessation of pain even after major stimuli. A topical analgesic agent is a substance which relieves pain without necessarily causing numbness, or which can relieve topical pain of minor nature, but not of a great degree (Fed. Register 44, 69768-69866, 1979). These drugs are therefore used to treat or prevent pain. For operations of peripheral and minor nature involving skin, like removal of superficial skin lesions and plastic surgery, or intradermal allergen testing, split skin grafting, treatment of painful ulcers, venipuncture - the ideal and painless way of anesthesia would be the topical application of local anesthetics.

The commercially available topical anesthetic preparations however, are not suitable for this purpose. Studies of Dalili and Adriani (Clin. Pharm. Ther. 12: 913-919, 1971) provided the first experimental evidence that manufactured preparations containing local anesthetics intended for use on the surface of the skin often lack efficacy. The preparations were tested on normal and ultraviolet light burned skin for the ability to block itching and pricking induced by electrical stimulation. The only effective preparation was one containing 20% benzocaine, the effect of which has disappeared within 60 seconds after it has

been wiped off the test site. The same authors pointed out several possible reasons for the lack of efficacy, such as low concentration of active ingredient, possible chemical change or interaction with other components and a pentration-preventing effect of the vehicles used (J. Adriani and H. Dalili. Anesth. Analg. 50: 834-841, 1971).

The most successful commercially available preparation for dermal anesthesia at the present is a lidocaine-prilocaine cream, first reported by Juhlin et al. (Acta Derm Venereol. 59: 556-559, 1979). The cream consists of the emulsion of 5% eutectic mixture of lidocaine and prilocaine bases (EMLA) in water, thickened with Carbopol^{R} (G.M.E. Ehrenstrom Reiz and SLA Reiz. Acta Anaesth. Scand. 26: 596-598, 1982). An application time of 60 minutes under occlusion is required to achieve complete anesthesia to pin-pricks, which lasts one to two hours (H. Evers et al. Br. J. Anaesth. 58: 997-1005, 1985).

In general, to achieve adequate local anesthesia of the skin excessive amounts of drug, prolonged application or invasive methods are required. For surgical anesthesia, the local anesthetic must be injected subcutaneously in order to reach sensory nerve endings lying in the dermis. When injecting a local anesthetic, pain is produced by the needle's penetration and by the deposition of the anesthetic solution. Distortion of the wound or performing the infiltration of large areas can also be problems in case of surgery (L. Juhlin, H. Evers, and F. Broberg. Acta Derm. Venereol. 60: 544-546, 1980).

In contrast to the skin, anesthesia of the mucous membrane covered surfaces can be produced by topical application of local anesthetics quickly and easily. However, rapid absorption of local anesthetic from these surfaces into the systemic circulation may cause short duration of local action, and possibly toxicity, since these drugs have low therapeutic ratios (J.A. Wildsmith, A.P. Rubin and D.B. Scott. Clin. Anaesth. 4: 527-537, 1986).

There is a need for a preparation that would be safe, yet effective on the unbroken skin, or on mucous membranes by providing a proper rate of premeation without discomfort or the risk of systemic reactions. The present invention can fulfill this need. Liposomes as drug carriers enhance penetration and localization of the drug applied topically (M. Mezei. in "Liposomes as Drug Carriers" ed. G. Gregoriadis, John Wiley & Sons, New York, 1988, page 663-677).

Local anesthetic agents have been previously encapsulated into liposomes in order to study their mechanism of action i.e. the interaction of local anesthetic with lipid bilayers, (Papahadjopoulos et al. Biochim. Biophys Acta 394: 504-519, 1975) however, no liposome encapsulated local anesthetics were tested or used for producing local anesthesia or analgesia prior to this invention. The first reports of this invention (Gesztes and Mezei, 47th International Congress of Pharmaceutical Sciences of F.I.P. Amsterdam, September 1, 1987; and Anesthesia and Analgesia, in press) relates to the superiority of liposome-

encapsulated tetracaine over the cream form tetracaine to produce anesthesia of the skin.

SUMMARY OF THE INVENTION

The present invention relates to the use of liposomes for improving the effect of local anesthetics by enhancing the penetration and localization of the anesthetic agents into and within the skin.

Local anesthetics as amphipathic agents are good candidates for entrapment in the phospholipid bilayers of the liposomes. Several anesthetic agents, e.g. benzocaine, lidocaine, prilocaine, lidocaine-prilocaine eutectic mixtures, tetracaine and dibucaine, was encapsulated into liposomes according to the method described by Mezei and Nugent (U.S. Patent 4,485,054, Nov. 27, 1984). In some cases, e.g. with benzocaine, lidocaine and dibucaine where the solubility would have restricted high enough concentration in the final product, the multiphase liposomal drug delivery system (Mezei, U.S. Patent Application, Serial No. 774.266) was utilized. Most of the time the base (and not the salt) of the anesthetic agent was used for preparing the liposomal product.

The following examples demonstrate the formulas and the activity of selected anesthetic agents in liposome versus ointment or cream form.

Example 1

Formula:

Tetracaine (base)	0.5 g
Soy phosphatidylcholine	7.0 g
Cholesterol	0.5 g
Stearic acid	0.7 g
Ethanol (95%)	10.0 ml
Propylene glycol	7.0 ml
Solution of sodium chloride (0.45%) and sodium bicarbonate (0.65%)	83.0 ml

Tetracaine, phosphatidylcholine, cholesterol and stearic acid were dissolved in chloroform:methanol 2:1 v/v in a pear-shaped flask, and glass beads (100 g) were added. The solvent was evaporated to dryness in a rotary evaporator under reduced pressure at 30°C, until a smooth, thin lipid film was obtained on the surface of the flask and glass beads. The film was hydrated with the aqueous phase containing 0.65% $NaHCO_3$, 0.45% NaCl, 10% ethanol and 7% propylene glycol in distilled water, by shaking for 30 minutes in a Lab-Line Orbit Environ-Shaker at 55°C. The liposomes were separated from the glass beads by filtering through a Buchner funnel without using a filter paper.

Example 2

Formula:

Lidocaine	2.0 g
Soy phosphatidylcholine	9.0 g
Tocopherol acetate	0.24 g
Hydorxypropylmethylcellulose	1.5 g
Aqueous solution of sodium chloride (0.45%) and sodium bicarbonate (0.65%)	100.0 ml

Lidocaine, soy phosphatidylcholine and tocopherol acetate were dissolved in chloroform:methanol (2:1) in a pear-shaped flasks containing 100 g of glass beads. The solvent was evaporated in a rotary evaporator under reduced pressure at 30° until a thin, smooth film of the residue was obtained on the surface of the glass beads and the wall of the flask. The resulting lipid film was hydrated by the sodium chloride, sodium bicarbonate solution in an environment shaker at 55° for 30 minutes. The hydroxypropylmethylcellulose was added within 5 seconds after the lipid film and aqueous solution were mixed.

Example 3

Dibucaine	1.0 g
Soy phosphatidylcholine	8.0 g
Tocopherol acetate	1.0 g
Hydroxypropylmethylcellulose	1.0 g
Tween-80	1.0 g
$CaCl_2$ solution 0.8 mM	100.0 ml

The method of preparation was similar as described above for example number 2; Tween-80 was added last to the liposomal product.

Example 4

In a manner similar to the preceding examples several other composition were prepared, characterized and tested, including

(a) different local anesthetic agents (e.g. benzocaine, prilocaine, lidocaine-prilocaine mixture) with various concentrations (0.5 to 5%);

(b) phosphatidylcholines of different origin and various concentrations (2-15%);

(c) cholesterol or tocopherol in different concentrations (0.5-5%);

(d) buffer solutions with various pH and electrolyte content;

(e) various viscosity inducing agents (e.g. methylcellulose, Carbopols, etc.) and

(f) various preservatives or antioxidant agents (e.g. benzoic acid, methyl and propyl paraben, BHA, benzylalcohol, etc.);

The efficacy of local anesthetic agents were tested in liposomal form against a commercial cream preparation or an ointment from of the same drug.

Evaluation of local anesthetic/analgesic activity.

The protocol for the human experiments was approved by the Ethics Committee for Human Research of the Faculty of Health Professions of Dalhousie University, Halifax, Canada. Healthy adult volunteers with no skin disorders or previous history of allergic sensitivity to local anesthetics were asked to participate in the study. Twelve subjects in each experimental group from 25 to 60 years of age were investigated following their written consent.

Tetracaine (0.5%) liposomes

Liposome preparation containing 0.5% tetracaine base (formula as example No. 1) and Pontocaine^{R} cream (tetracaine

hydrochloride cream U.S.P., equivalent to 1% tetracaine base, manufactured by Winthrop Laboratories) were compared. A 0.2 ml volume of the liposomal preparation was applied to a 10 cm^2 area marked by ink on the volar surface of one forearm of the volunteers and covered with a Blenderm^R tape to form an occlusive dressing. A sample of Pontocaine^R cream was applied in the same manner to the other arm. The samples of the liposomal and commercial preparation were randomly numbered, and the number of applied preparations recorded for each subject. The identity of the preparations was not known for the subjects or for the evaluator to maintain the "double blind" study design.

The samples had been applied for 30 minutes in the first group of volunteers and 60 minutes in the second group. After this time interval the covering tape was removed and the tested area wiped dry with a tissue paper. Onset and duration of anesthesia at the test sites was tested with the pin-prick technique, described in detail by Lubens et al. (Am. J. Dis. Child. 128: 192-194, 1974). Each skin test area was pricked ten times using a relatively blunt sterile needle, which allowed the subject to discriminate between the perception of touch and pain. Ten painless pricks indicated complete anesthesia. Sensitivity was confirmed by pin-pricking near to the test site areas before application of the samples to be tested. Testing score indexes were obtained from the volunteers by noting the numbers of painfree pin-pricks out of the 10 in both test areas. Testing was done immediately after the preparations had been removed from the test site, and then at 30 min., 1h, 2h, and 4h afterwards. Results are indicated in Tables 1 and 2.

The liposome preparation containing 0.5% tetracaine base was effective in producing dermal anesthesia. After the onset of anesthesia the perception of pain was greatly reduced; although the pressure could be felt. The perception of cold was also observed to disappear at the "numb" test sites (by testing with a cold metal rod). Sensitivity of nerve fibers conveying the sensations of pain, cold, warmth, touch and deep pressure to local anesthetic action is differential. This is correlated with the fiber diameter, that increases from the fibers conveying the sensation of pain to those conveying deep pressure. Pain fibers are the first to be blocked, followed by sensations of cold, warmth, touch and deep pressure. Probably the absorbed doses were high enough only to block the pain and cold fibers, having no or little effect on touch or pressure sensations.

Duration of application influenced the intensity and duration of the effect. On removal of the preparation after 30 minutes of application, the anesthesia was less pronounced, than after one hour of application. In both cases the anesthesia improved with time. A maximum was reached in the 30 minutes and 1 hour application time groups two hours after removal of the preparation at an average painless score of 8.25 and 9.5 respectively. This level of anesthesia as maintained until the end of the experiments. Tests were conducted only up to 4 hours after removal of the preparations, but the anesthesia as reported by the volunteers to persist longer, from 5 to 8 hours, depending on the application time. Considerable interindividual variations were observed in the onset time of action. Painless scores in

the 30 minutes and 1 hour application time groups at the time of removal were at or above 7 in 25% and 50% of all the subjects (N=12), respectively. Pontocaine cream, the control preparation, was found to be ineffective, in agreement with findings of Dalili and Adriani (Cin. Pharm. Ther. 12: 913-919, 1971).

Statistical analysis of the data by paired t-tests indicated a statistically highly significant difference in favor of the liposomal tetracaine over the commercial preparation (Tables 1 and 2).

Liposomes with 2% lidocaine (preparation as example No. 2) were compared first to a placebo, which consisted of "empty" liposomes with the same composition as that of the active preparation (example No. 2) but without lidocaine.

Comparison of the 2% lidocaine liposomes was also carried out to a control dosage form, which contained 2% lidocaine incorporated in Dermabase^{R} as the vehicle. In both groups the length of application of liposomal and control preparations was one hour.

The effect of the 2% lidocaine liposomes compared to the placebo as measured by the painless scores is shown in Table 3. Similarly to the tetracaine liposomal preparation, lidocaine encapsulated in liposomes could produce anesthesia in the intact skin. The pain and cold sensations have been greatly reduced but not the perception of pressure. The intensity of the effect

again increased after the removal of the preparation, to reach its maximum one hour later. The differences between the placebo and the liposome-encapsulated lidocaine preparation were statistically significant at every time point (Table 3). The results were similar, when liposomal lidocaine was compared to lidocaine in Dermabase^{R} (Table 4).

CLAIMS

1. The use of liposomes for improving the effect of local anesthetics or analgesics applied topically

2. The liposomes of claim 1 can be:
   a) multilamellar lipid vesicles
   b) unilamellar lipid vesicles, and
   c) classified as multiphase liposomal drug delivery system

3. The liposomal local anesthetic or local analgesic products (of claim 1) can contain:
   a) any biologically active agents that is classified as local anesthetic or local analgesic
   b) phospholipids of different origin and in different concentration
   c) cholesterol other lipids and/or tocopherol in various concentrations

d) auxiliary agents, e.g. ethanol, glycerin, propylene, glycol, viscosity inducing agents, surface active agents preservatives, antioxidants, etc.

e) the aqueous phase can be distilled water or buffer with various pH, and electrolyte content

Table 1. Mean painless scores at different times of observation after 30 minutes application of 0.5% tetracaine liposome preparation and Pontocaine cream
Number of volunteers=12
Statistical analysis by paired t-tests

Time	Liposome preparation Mean	SD	Pontocaine cream Mean	SD	p
at removal	2.75	3.25	0.25	1.73	0.0644
30 min	5.50	3.94	1.08	1.98	0.0117
1 hour	6.75	3.28	1.08	1.68	<0.0001
2 hours	8.25	2.45	1.08	1.31	<0.0001
4 hours	8.33	2.31	0.25	0.62	<0.0001

Table 2. Mean painless scores at different times of observation after 1 hour application of 0.5% tetracaine liposome preparation and Pontocaine cream
Number of volunteers=12
Statistical analysis by paired t-tests

Time	Liposome preparation		Pontocaine cream		P
	Mean	SD	Mean	SD	
at removal	6.25	3.65	0.08	0.29	<0.0001
30 min	8.08	2.27	0.41	0.99	<0.0001
1 hour	8.83	1.47	0.25	0.62	<0.0001
2 hours	9.50	0.67	0.33	1.15	<0.0001
4 hours	8.75	1.48	0.16	0.57	<0.0001

Table 3. Mean painless scores at different times of observation after 1 hour application of 2% lidocaine liposome preparation and placebo
Number of volunteers=12
Statistical analysis by paired t-tests

Time	Liposome preparation		Placebo		P
	Mean	SD	Mean	SD	
at removal	4.08	4.42	1.08	1.51	0.0337
30 min	6.08	4.14	1.33	1.92	0.0040
1 hour	7.25	3.86	2.08	2.23	0.0040
2 hours	6.16	3.35	1.58	2.81	0.0062
3 hours	5.33	3.17	1.16	2.04	0.0042

Table 4. Mean painless scores at different times of observation after 1 hour application of 2% lidocaine in liposomes and Dermabase (control)
Number of volunteers=5
Statistical analysis by paired t-tests

Time	Liposome preparation		Dermabase (control)		P
	Mean	SD	Mean	SD	
at removal	6.2	3.56	1.8	2.49	0.103
30 min	7.4	3.71	2.6	1.67	0.018
1 hour	9.8	0.45	3.6	0.89	<0.001
2 hours	8.6	1.14	3.2	1.30	<0.001
3 hours	4.6	3.13	2.2	2.17	0.051

Exhibit 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

United States Patent No.: 4,937,078

Issued: June 26, 1990

Inventors: Michael Mezei and Adrienn Gesztes

For: LIPOSOMAL LOCAL ANESTHETIC
AND ANALGESIC PRODUCTS

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

GRANT OF POWER OF ATTORNEY

The undersigned:

MEZEI ASSOCIATES LIMITED, Nova Scotia, Canada, a corporation of Canada

hereby appoint(s) the following persons as agent:

BALANCIA, Victor; BEARDELL, Louis W.; BIRD, Donald J.; DOYLE, Kathryn; GAYBRICK, Robert J.; GOLUB, Daniel H.; GOODWYN, R. Tyler; KOKULIS, Paul N.; LAUB, David W.; MCCUTCHEON, Nathan W.; SMITH, John G.; ZELE, John D; BOSWELL, Mary Jane; BRETSCHER, Carl P.; HAYDEN, Christopher G.; TUSCAN, Michael S.; VEITENHEIMER, III, Erich E.; WEIMAR, Elizabeth C.; ALVAREZ, Raquel M; ANCHELL, Scott J.; BATTISTA Jr., William G.; ANTONELLI, Arthur; BALTAZAR, David J.; BASSON, Kent E.; CARLINEO, Daniel S.; DAVIS, Kenneth, J.; DIETZE, Paul E.; FANELLI, Dean L.; FOSTER, William S.; FOURNIER, Paul A.; GOODELL, Robert J.; HALLIDAY, Christopher I.; HAO, Victoria B.; HARDY, David B.; HOLLINGSHEAD, Robert J.; HOPKINS, Martha J.; KOENIGBAUER, Fabian M.; LEE, Sunwoo; LOWEN, Gregory T.; MAURER, Eric J.; MONIN Jr., Donald L.; MCLEOD, Bonnie W.; NELSON, Thomas E.; PARK, Collin W.; PHILLIPS, Ralph; REED, James L.; ROBINSON, Angela; SCHWARZ, Steven; SISTARE, Peter J.; SMYTH, Robert J.; SOSSONG, Thomas; SULLIVAN, Mark J.; TA, Khoi; TAYLOR, Todd P.; TENG, Sally P.; THURSTON Alisa L.; WEISBERG, Alison; YOSHIMURA, Masao; ZISKA, Suzanne E. and all of MORGAN, LEWIS & BOCKIUS LLP, 1111 Pennsylvania Avenue, NW, Washington, DC 20004 United States of America

for the purpose of obtaining a patent term extension for United States patent no. 4,937,078. Assignee further directs that all correspondence for this matter be addressed to the Customer Number given below:

Customer Number: 009629

Please direct all telephone inquiries to:

Paul E. Dietze
Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Telephone: (202) 739-5667

The undersigned certifies that he is empowered to act on behalf of **MEZEI ASSOCIATES LIMITED** in this matter. The undersigned hereby certifies that **MEZEI ASSOCIATES LIMITED** has the entire right, title and interest in the above-identified United States patent by virtue of an assignment recorded at reel 005044, frame 0743 on October 18, 1988 from Adrienn Gesztes and an assignment recorded at reel 005044, frame 0741 on October 18, 1988 from Michael Mezei.

Signature for Applicant: _____

Title: PRESIDENT

Address: P.O. Box 2255
HALIFAX Nova Scotia B3J-3C8
CANADA

Date: June 25/04

Exhibit 3

Veterinary Package Insert

SURPASS™
(1% diclofenac sodium)
Topical Anti-Inflammatory Cream for Use in Horses

CAUTION
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
SURPASS™ topical cream contains 1% diclofenac sodium. Diclofenac is a nonsteroidal anti-inflammatory drug of the phenylacetic acid class. The chemical name for diclofenac is sodium [o- (2,6-dichloroanilino)phenyl]acetate. The empirical formula is $C_{14}H_{10}Cl_2NNaO_2$ and the molecular weight is 318.13. SURPASS topical cream contains 1% diclofenac sodium in a base composed of Phospholipon 90H, propylene glycol, alcohol (5.94%), vitamin E acetate, benzethonium chloride and purified water in a liposomal formulation.

INDICATIONS
SURPASS topical cream is indicated for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal and proximal interphalangeal (hock, knee, fetlock and pastern) joints in horses.

DOSAGE AND ADMINISTRATION
Always provide the Client Information Sheet with the prescription.

Dosage: Apply a five-inch (5") ribbon of SURPASS topical cream twice daily over the affected joint for up to ten days.

Administration: Wear rubber gloves to prevent absorption into the hands. Rub the cream thoroughly into the hair covering the joint until it disappears.

CONTRAINDICATIONS
SURPASS topical cream is contraindicated in animals with known hypersensitivity to diclofenac.

WARNINGS
Not for horses intended for human consumption.

User Safety: Keep out of reach of children. Not for human use. Consult a physician in case of accidental ingestion by humans. Wear gloves to prevent absorption into the hands. Direct contact with the skin should be avoided. If contact occurs, the skin should be washed immediately with soap and water.

Animal Safety: **For topical use in horses only.** Owners should be advised to observe for signs of potential drug toxicity (see INFORMATION FOR OWNER OR PERSON TREATING ANIMAL and ADVERSE REACTIONS).

PRECAUTIONS
Exceeding the recommended dosage or treating multiple joints may increase plasma concentrations of diclofenac (see ANIMAL SAFETY). The systemic effects of excess diclofenac doses that exceed the recommended label amount and duration have not been evaluated.

Horses should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data before and periodically during administration of any NSAID. Owners should be advised to observe for signs of potential drug toxicity (see INFORMATION FOR OWNER OR PERSON TREATING ANIMAL).

Treatment with SURPASS should be terminated if signs such as inappetence, colic, fecal abnormalities, anemia or depression are observed.

As a class, NSAIDs may be associated with gastrointestinal and renal toxicity. When NSAIDs inhibit prostaglandins that cause inflammation, they may also inhibit prostaglandins that maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or preexisting disease more often than in healthy patients. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular and/or hepatic dysfunction.

Studies to determine the effect of SURPASS when administered concomitantly with other drugs have not been conducted. Since many NSAIDs possess the potential to induce gastric ulceration, concomitant use of SURPASS with any other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided. Drug compatibility should be monitored closely in patients receiving adjunctive therapy.

The safety of SURPASS has not been investigated in breeding, pregnant or lactating horses, or in horses under one year of age.

ADVERSE REACTIONS
During the field study, one diclofenac-treated horse developed colic on day four of the study and responded to symptomatic treatment. One placebo-treated horse exhibited mildly jaundiced mucous membranes on day five. Adverse reactions during the

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Client Information Sheet

SURPASS™
(1% diclofenac sodium)
Topical Anti-Inflammatory Cream for Use in Horses

This summary contains important information about SURPASS™ topical cream. You should read this information before treating your horse with SURPASS. This sheet of information is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you have any questions about this information or to learn more about SURPASS.

1. What is SURPASS topical cream?
SURPASS topical cream contains 1% diclofenac sodium. Diclofenac is a prescription non-narcotic, nonsteroidal anti-inflammatory drug (NSAID) that controls pain. Diclofenac is used for the control of pain and inflammation associated with osteoarthritis (OA) in hock, knee, fetlock or pastern joints in horses.

2. What kind of results can I expect when my horse is being treated with SURPASS?
Osteoarthritis is a painful condition caused by the progressive deterioration of the cartilage, accompanied by changes in the bone and soft tissues of the joint. This disease is characterized by pain and loss of function of the affected joint.

While SURPASS is not a cure for osteoarthritis, it does control the pain and inflammation associated with OA and increases the horse's mobility. The response to SURPASS will vary from horse to horse. In most horses, maximum improvement is seen in less than one week.

3. Which horses should not receive treatment with SURPASS?
SURPASS is for topical use in horses only. SURPASS should not be used in horses exhibiting allergic reactions to diclofenac. SURPASS is not for use in horses intended for food. The safety of SURPASS has not been determined in horses less than one year of age, in horses used for breeding, pregnant mares, or mares nursing foals.

4. How do I apply SURPASS to my horse?
Wear gloves to prevent absorption into the hands. Direct contact with the skin should be avoided. If contact occurs, the skin should be washed immediately with soap and water. Apply a five-inch (5") ribbon of SURPASS twice daily over the affected joint for up to ten days. Rub it thoroughly into the hair covering the joint until it disappears.

5. What should I tell my veterinarian?
Tell your veterinarian if your horse has experienced allergic reactions to diclofenac or other medications. Tell your veterinarian if your horse is pregnant or nursing a foal, or if you intend to breed the horse. Tell your veterinarian if your horse has ever been diagnosed with an ulcer.

6. What possible side effects may occur in my horse's therapy?
Horses should undergo a thorough history and physical examination by a veterinarian before the initiation of any SURPASS therapy.

safety study included a gastric ulcer in one horse that received 5.6X the recommended dosage, diarrhea and uterine discharge in one horse that received 2.8X the recommended dosage, and weight loss in four of the six horses in the 5.6X dosage group.

To report suspected adverse reactions, to obtain a Material Safety Data Sheet or for technical assistance, call 1-800-374-8006.

INFORMATION FOR OWNER OR PERSON TREATING ANIMAL
Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with NSAID intolerance. Adverse reactions may include weight loss, colic, diarrhea, or icterus. Serious adverse reactions associated with this drug class can occur without warning and, in rare situations, result in death. Owners should be advised to discontinue NSAID therapy and contact their veterinarian immediately if signs of intolerance are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care is initiated.

CLINICAL PHARMACOLOGY
Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties. The mechanism of action of diclofenac, like other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity.

EFFECTIVENESS
In a controlled field study, 82 horses with osteoarthritis were treated with SURPASS (42 horses) or placebo (40 horses). Lameness examinations were performed in horses with osteoarthritis associated with the tarsal, carpal, metacarpophalangeal, metatarsophalangeal and proximal interphalangeal joints. Investigators were masked to treatment. Investigators and owners were instructed to apply the test article over the affected joint twice daily (BID) for five days. Actual doses received by individual horses were calculated using tube weight measurements. The mean dose applied during the study was 73 mg per application. Average lameness scores showed statistically significant improvement following treatment with SURPASS topical cream.

One diclofenac-treated horse developed colic and responded to symptomatic treatment on day four of the study. Day five bloodwork for the horse that colicked showed decreases in RBC, Hb and HCT, with an increase in PMNs, compared to pretreatment values. One placebo-treated horse exhibited mildly jaundiced mucous membranes on day five. No other adverse reactions were noted during the study.

ANIMAL SAFETY
A controlled safety study was conducted with SURPASS topical cream. Four groups of six healthy adult horses received 0, 0.6, 1.7 or 2.8X the recommended daily dose for twenty-eight days. The daily dose was divided into two applications on day one of the study. For the remainder of the study, the entire daily dose was given at one time on 0, 1, 3 or 5 joints (tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints), depending on the dosage group. The control group of six horses was sham-dosed by rubbing the joints daily for twenty-eight days. An additional study group evaluated six horses that received 5.6X the recommended daily dose of SURPASS topical cream distributed over five joints on a single day. This dose group was observed for fourteen days without additional treatment.

Clinical examinations, hematology, serum chemistry, synovial fluid analyses, gross necropsy and histopathology were performed. At necropsy, one horse in the 5.6X group had a glandular gastric ulcer. A horse in the 2.8X group had diarrhea and uterine discharge throughout the study. Four of the six horses in the 5.6X group lost weight during the study.

Dose-dependent increases in diclofenac plasma concentrations were detected in horses in the 1.7X and 2.8X treatment groups.

STORAGE INFORMATION
Store at up to 25°C (77°F). Protect from freezing.

HOW SUPPLIED
SURPASS topical cream is white to pinkish-white and is packaged in 124-gram trilaminate tubes.

NADA #141-186. Approved by FDA.

SURPASS is a trademark of IDEXX Pharmaceuticals, Inc.

Manufactured for: IDEXX Pharmaceuticals, Inc.
Greensboro, North Carolina 27410 USA

Manufactured under U.S. Patent No. 4,937,078.

IPI/DIC/PI/19 3/04 000100

IDEXX LABORATORIES

Greensboro, NC 27410 USA

Using more than the recommended amount of SURPASS (for example, by treating multiple joints) has not been tested and is not recommended. Excessive doses to the skin have been shown to enter the bloodstream and this may increase the risk of side effects. Adverse reactions associated with NSAIDs may include weight loss, colic, diarrhea, or yellowing of the gums, skin, or whites of the eyes (jaundice). Serious adverse reactions associated with this drug class can occur without warning and, in rare situations, result in death. Discontinue the use of SURPASS and contact your veterinarian immediately if these signs are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care, if appropriate, is initiated.

7. What precautions should I take before administering SURPASS topical cream?
Wear gloves to prevent absorption into the hands. Direct contact with the skin should be avoided. If contact occurs, the skin should be washed immediately with soap and water.

SURPASS topical cream should only be applied to horses. Keep SURPASS and all medications out of the reach of children. SURPASS is not for human use. Contact a physician in case of accidental ingestion by people.

8. Can SURPASS be given with other medications?
SURPASS should not be given with any other anti-inflammatory drugs, such as other NSAIDs (for example, aspirin, phenylbutazone, flunixin) and corticosteroids (for example, cortisone, prednisone, dexamethasone, triamcinolone). Tell your veterinarian about all medicines that you are planning to administer in addition to SURPASS. These should include other medications that you can obtain without a prescription.

9. How should I store SURPASS?
Store at up to 25°C (77°F). Protect from freezing. Keep SURPASS and all medications out of reach of children.

10. What else should I know about SURPASS?
This document provides a summary of information about SURPASS. If you have questions or concerns about SURPASS or osteoarthritis pain, talk to your veterinarian.

As with all prescription medications, SURPASS should only be administered to the patient for whom it was prescribed, and should only be used as prescribed.

To report a suspected adverse reaction, call 1-800-374-8006.

SURPASS is a trademark of IDEXX Pharmaceuticals, Inc.

SURPASS is manufactured for:
IDEXX Pharmaceuticals, Inc.
Greensboro, North Carolina 27410 USA

Manufactured under U.S. Patent No. 4,937,078.

IPI/DIC/CI/11 3/04 000100

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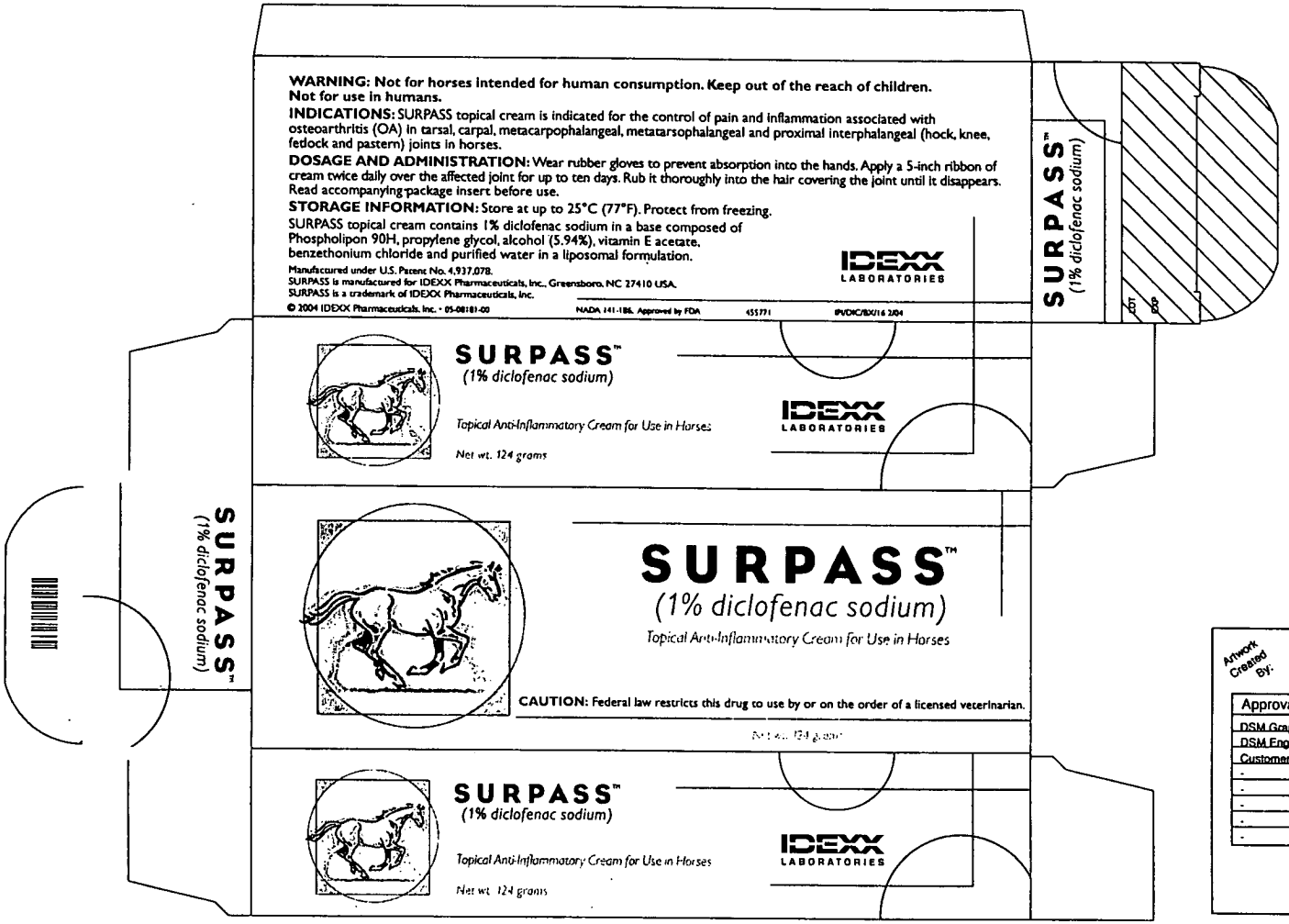
Greensboro, NC 27410 USA

455771
Tube Carton - Surpass Cream 4.0 oz.
Size: 2-1/2" x 1-5/8" x 7-1/2"

Colors:

C0/M0/Y27/K11	C11/M0/Y0/K64	C6/M87/Y0/K69	C0/M60/Y100/K34	C6/M6/Y34/K0	Black
Tan	Gray	Brown	Rust	Beige	



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Package Engineering Department

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DSM Engineer		
Customer Approvals:		
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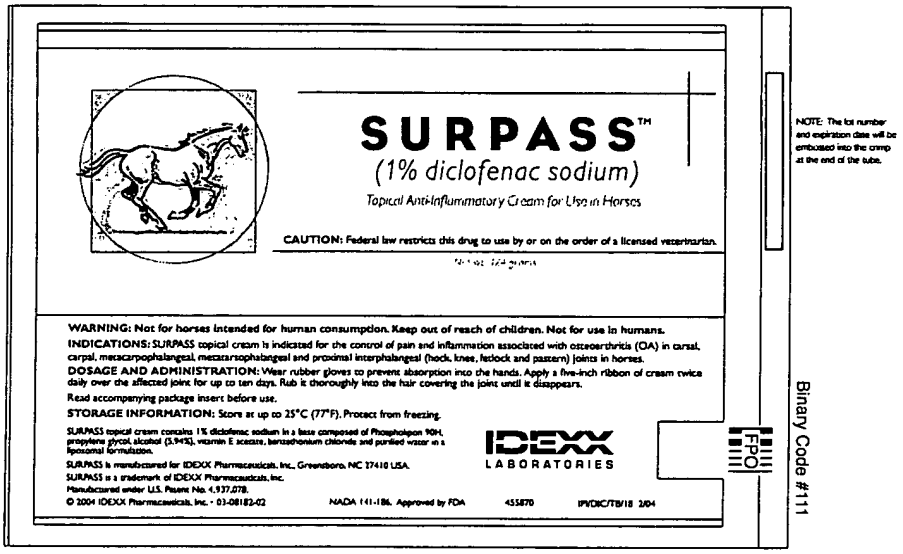
DSM

455870
Tube Glaminate - Surpass Cream 4.0 oz.
Size: 4.743" x 6 - 25/32"
Colors:

C0/M0/Y27/K11	C11/M0/Y0/K64	C6/M87/Y0/K69	C0/M60/Y100/K34	C6/M6/Y34/K0	Black
Tan	Gray	Brown	Rust	Beige	



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Approvals	Signature	Date
DSM Graphics Specialist		
DSM Engineer		
Customer Approvals:		
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DSM

587293
Display Box - Surpass Cream 4.0 oz.
Size: 5-1/8" x 5-1/16" x 7-21/23"

Colors:

C0/M0/Y27/K11	C11/M0/Y0/K84	C6/M87/Y0/K89	C0/M60/Y100/K34	C6/M6/Y34/K0	Black
Tan	Gray	Brown	Rust	Beige	

DSM Pharmaceuticals, Inc.
Package Engineering Department

Approvals	Signature	Date
DSM Graphics Specialist		
DSM Engineer		
Customer Approvals:		

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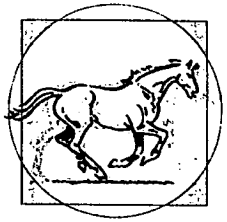
SURPASS™
(1% diclofenac sodium)



SURPASS™
(1% diclofenac sodium)

Topical Anti-inflammatory Cream for Use in Horses

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

WARNING: Not for horses intended for human consumption. Keep out of reach of children. Not for use in humans.

Contents: Six 124-gram tubes

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SURPASS™
(1% diclofenac sodium)

Topical Anti-inflammatory Cream for Use in Horses

Contents: Six 124-gram tubes

IDEXX LABORATORIES

NADA 141-186, Approved by FDA

SURPASS™
(1% diclofenac sodium)

IDEXX LABORATORIES

03-6119-00

SURPASS™
(1% diclofenac sodium)

INDICATIONS: SURPASS topical cream is indicated for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal and proximal interphalangeal (hock, knee, fetlock and pastern) joints in horses.

CONTENTS: Six 124-gram tubes

STORAGE INFORMATION: Store at up to 25°C (77°F). Protect from freezing.

SURPASS topical cream contains 1% diclofenac sodium in a base composed of Phospholipon 90H, propylene glycol, alcohol (5.94%), vitamin E acetate, benzethonium chloride and purified water in a liposomal formulation.

Manufactured under U.S. Patent No. 4 937 078

SURPASS is manufactured for IDEXX Pharmaceuticals, Inc., Greensboro NC 27410 USA

SURPASS is a trademark of IDEXX Pharmaceuticals, Inc.

98-09315-00

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PHDC-06/17 3M
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98-09315-00 587293

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Exhibit H

United States Patent [19]

Mezei et al.

[11] **Patent Number: 4,937,078**

[45] **Date of Patent: Jun. 26, 1990**

[54] **LIPOSOMAL LOCAL ANESTHETIC AND ANALGESIC PRODUCTS**

[75] Inventors: **Michael Mezei, Halifax, Canada; Adrienn Gesztes, Budapest, Hungary**

[73] Assignee: **Mezei Associates Limited, Nova Scotia, Canada**

[21] Appl. No.: **236,724**

[22] Filed: **Aug. 26, 1988**

[51] **Int. Cl.**[5] **A61K 37/22**

[52] **U.S. Cl.** **424/450; 424/1.1; 514/817; 514/818**

[58] **Field of Search** 424/450, 1.1; 514/817, 514/818

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,645,911	2/1972	van Vesauw et al.	264/4.6
3,804,776	4/1974	Yazawa et al.	427/213.3
4,016,100	4/1977	Suzuki et al.	264/4.3
4,048,310	9/1977	Chen et al.	514/873 X
4,089,801	5/1978	Schneider	264/4.1
4,235,871	11/1980	Papahadjopoulous et al.	264/4.6 X
4,342,826	8/1982	Cole	436/7
4,438,052	3/1984	Weder et al.	264/4.6
4,485,054	11/1984	Mezei et al.	264/4.6
4,532,089	7/1985	MacDonald	264/4.3
4,649,047	3/1987	Kaswan	424/78
4,721,612	1/1988	Janoff et al.	424/450
4,725,442	2/1988	Haynes	424/450
4,746,508	5/1988	Carey et al.	424/88

FOREIGN PATENT DOCUMENTS

00084898	8/1983	European Pat. Off. .
85/306641.8	4/1987	European Pat. Off. .
3335701A1	4/1981	Fed. Rep. of Germany .
WO85/03640	8/1985	PCT Int'l Appl. .
2050833A	1/1981	United Kingdom .

OTHER PUBLICATIONS

Bangham et al., "Diffusion of Univalent Ions Across the Lamellae of Swollen Phospholipids", J. Mol. Biol. 13:238–252 (1965).

Bangham et al., "Osmotic Properties and Water Permeability of Phospholipid Lipid Crystals, Chem. Phys. Lipids, 1:225–246 (1967).

Batzri et al., "Single Bilayer Liposomes Prepared Without Sonication", Biochim. et Biophys. Acta, 298:1015–1019.

Bangham et al., "Preparation and Use of Liposomes as Models of Biological Membranes", Methods in Membrane Biology, 6 (London 1974).

Papahadjopoulos et al, "Effects of Local Anesthetics on Membrane Properties", Biochim et Biophys. Acta, 394:504–519 (1975).

Theoharides, "Liposomes as Carriers of Biologically Active Molecules", *Folia Bioch. et Biol. Graeca*, Special Issue, vol. XIV, pp. 11–21 (1978).

Mezei et al., "Liposomes–A Selective Drug Delivery System for the Topical Route of Administration", Life Sciences, vol. 26, pp. 1473–1477 (1980).

Okano et al., "Duration of the Local Anesthetic Action of Dibucaine by Liposomes and Its Mechanism", Yakugaku Zasshi, vol. 100 (11), pp. 1097–1103 (1980).

Chemical Abstracts, vol. 97, No. 22 (1982), Abstract No. 188156k.

"The Effect of Local Anaesthetics on the Osmotic Fragility of Liposomes", Biochemical Pharmacology, vol. 31, No. 18, pp. 2999–3000 (1982).

Mezei et al., "Liposomes—A Selective Drug Delivery System for the Topical Route of Administration: Gel Dosage Form", *J. Pharm. Pharmacol.*, 1982, 34:473–474.

Cecil–"Textbook of Medicine", vol. 1 (1982), pp. 1276–1278.

Seelig, Biochimica et Biophysica Acta 899 (1987) 196–204.

Kuroda et al., Biochimica et Biophysica Acta 903 (1987) 395–410.

Bianconi et al., Biochemical and Biophysical Research Communications, vol. 152(1):344–350 (1988).

Seelig et al., Biochimica et Biophysica Acta 939 (1988) 267–276.

Gesztes et al., Topical Anesthesia of the Skin by Liposome-Encapsulated Tetracaine, Anesth Analg, vol. 67:1079–1081 (1988).

Mezei, "Liposomes in the Topical Application of Drugs: a Review", Liposomes as Drug Carriers, edited by G. Gregoriadis, John Wiley & Sons Ltd., NY (1988) pp. 663–677.

Ohki, Biochimica et Biophysica Acta, 777 (1984) 56–66.

Schlieper et al., Biochemical Pharmacology, vol. 32, No. 5, pp. 799–804 (1983).

Simmonds et al., Biochimica et Biophysica Acta, 813 (1985) 331–337.

Krause-Friedmann et al., Biochimica et Biophysica Acta, 799 (1984) 195–198.

Dalili et al. Clin. Pharm. Ther., 12:9–919 (1971).

Adriani et al., Anesth. Analg., 50:834–841 (1971).

Juhlin et al., Acta Dermatovener 59:556–559 (1979).

Wildsmith et al., Clinics in Anaesthesiology, 4:527–537 (1986).

Ehrenstrom Reiz et al., Acta Anaesth. Scand. 26:596–598 (1982).

Evers et al., Br. J. Anaesth. 58:997–1005 (1985).

Juhlin et al., Acta Dermatovener 60:544–546 (1980).

Primary Examiner—Ellis P. Robinson

Assistant Examiner—P. L. Prater

Attorney, Agent, or Firm—Banner, Birch, McKie & Beckett

[57] **ABSTRACT**

Liposome encapsulated local anesthetic or analgesic agents when applied to skin or mucous membranes provided greater local anesthesia and analgesia than the same agents incorporated in conventional vehicles i.e., ointment, cream or lotion.

14 Claims, No Drawings

LIPOSOMAL LOCAL ANESTHETIC AND ANALGESIC PRODUCTS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method for providing local anesthesia using liposomal encapsulated anesthetic and analgesic drugs.

2. Description of Related Art

Liposomes are lipid vesicles composed of membrane-like lipid layers surrounding aqueous compartments. Liposomes are widely used to encapsulate biologically active materials for a variety of purposes, e.g. they are used as drug carriers. Depending on the number of lipid layers, size, surface charge, lipid composition and methods of preparation various types of liposomes have been utilized.

Multilamellar lipid vesicles (MLV) were first described by Bangham, et al., (J. Mol. Biol. 13:238–252, 1965). A wide variety of phospholipids form MLV on hydration. MLV are composed of a number of bimolecular lamellar interspersed with an aqueous medium. The lipids or lipophilic substances are dissolved in an organic solvent. The solvent is removed under vacuum by rotary evaporation. The lipid residue forms a film on the wall of the container. An aqueous solution generally containing electrolytes and/or hydrophilic biologically active materials are added to the film. Agitation produces larger multilamellar vesicles. Small multilamellar vesicles can be prepared by sonication or sequential filtration through filters with decreasing pore size. Small unilamellar vesicles can be prepared by more extensive sonication. An improved method of encapsulating biologically active materials in multilamellar lipid vesicles is described in U.S. Pat. No. 4,485,054.

Unilamellar vesicles consist of a single spherical lipid bilayer entrapping aqueous solution. According to their size they are referred to as small unilamellar vesicles (SUV) with a diameter of 200 to 500 A; and large unilamellar vesicles (LUV) with a diameter of 1000 to 10,000 A. The small lipid vesicles are restricted in terms of the aqueous space for encapsulation, and thus they have a very low encapsulation efficiency for water soluble biologically active components. The large unilamellar vesicles, on the other hand, encapsulate a high percentage of the initial aqueous phase and thus they can have a high encapsulation efficiency. Several techniques to make unilamellar vesicles have been reported. The sonication of an aqueous dispersion of phospholipid results in microvesicles (SUV) consisting of bilayer or phospholipid surrounding an aqueous space (Papahadjopoulos and Miller, Biochem. Biophys. Acta., 135: 624–238, 1968). In another technique (U.S. Pat. No. 4,089,801) a mixture of a lipid, an aqueous solution of the material to be encapsulated, and a liquid which is insoluble in water, is subjected to ultrasonication, whereby liposome precursors (aqueous globules enclosed in a monomolecular lipid layer), are formed. The lipid vesicles then are prepared by combining the first dispersion of liposome precursors with a second aqueous medium containing amphiphilic compounds, and then subjecting the mixture to centrifugation, whereby the globules are forced through the monomolecular lipid layer, forming the biomolecular lipid layer characteristic of liposomes.

Alternate methods for the preparation of small unilamellar vesicles that avoid the need of sonication are

the ethanol injection technique (S. Batzri and E. E. Korn, Biochem. Biophys. Acta. 298: 1015–1019, 1973) and the ether injection technique (D. Deamer and A. D. Bangham, Biochem. Ciophys. Acta. 443: 629–634, 1976). In these processes, the organic solution of lipids is rapidly injected into a buffer solution where it spontaneously forms liposomes—of the unilamellar type. The injection method is simple, rapid and gentle. However, it results in a relatively dilute preparation of liposomes and it provides low encapsulation efficiency. Another technique for making unilamellar vesicles is the so-called detergent removal method (H. G. Weder and O. Zumbuehl, in "Liposome Technology": ed. G. Gregoriadis, CRC Press Inc., Boca Raton, Florida, Vol. I, Ch. 7, pg. 79–107, 1984). In this process the lipids and additives are solubilized with detergents by agitation or sonication yielding defined micelles. The detergents then are removed by dialysis.

Multilamellar vesicles can be reduced both in size and in number of lamellae by extrusion through a small orifice under pressure, e.g., in a French press. The French press (Y. Barenholz; S. Amselem an D. Lichtenberg, FEBS Lett. 99: 210–214, 1979), extrusion is done at pressures of 20,000 lbs/in at low temperature. This is a simple, reproducible, nondestructive technique with relatively high encapsulation efficiency, however it requires multilamellar liposomes as a starting point, that could be altered to oligo- or unilamellar vesicles. Large unilamellar lipid vesicles (LUV) can be prepared by the reverse phase evaporation technique (U.S. Pat. No. 4,235,871, Papahadjopoulos). This technique consists of forming a water-in-oil emulsion of (a) the lipids in an organic solvent and (b) the substances to be encapsulated in an aqueous buffer solution. Removal of the organic solvent under reduced pressures produces a mixture which can then be converted to the lipid vesicles by agitation or by dispersion in an aqueous media.

U.S. Pat. No. 4,016,100, Suzuki et al., describes still another method of entrapping certain biologically active materials in unilamellar lipid vesicles by freezing an aqueous phospholipid dispersion of the biologically active materials and lipids. All the above liposomes, made prior to 1983, can be classified either as multilamellar or unilamallar lipid vesicles. A newer type of liposomes is referred to as multivesicular liposomes (S. Kim, M. S. Turker, E. Y. Chi, S. Sela and G. M. Martin, Biochim. Biophys. Acta. 728: 339–348, 1983). The multivesicular liposomes are spherical in shape and contain internal granular structures. A lipid bilayer forms the outermost membrane and the internal space is divided up into small compartments by bilayer septrum. This type of liposomes required the following composition: an amphiphatic lipid with net neutral charge, one with negative charge, cholesterol and a triacylglycerol. The aqueous phase containing the material to be encapsulated is added to the lipid phase which is dissolved in chloroform and diethyl ether, and a lipid-in-water emulsion is prepared as the first step in preparing multivesicular liposomes. Then a sucrose solution is shaken with the water-in-lipid emulsion; when the organic solvents are evaporated liposomes with multiple compartments are formed.

For a comprehensive review of types of liposome and methods for preparing them refer to a recent publication "Liposome Technology" Ed. by G. Gregoriadis., CRC Press Inc., Boca Raton, Florida, Vol. I, II, and III 1984.

Liposomes, vesicles of phospholipid membranes, have been studied in recent years as a way of altering the pharmacokinetic properties of encapsulated drugs. A few studies have focused on their potential as drug carriers in topical preparations, for example involving corticosteriods, econazole, progesterone and methotrexate. Liposomal formulations of these materials were found which when applied topically delivered more of these drugs into the skin than conventional vehicles, (enhanced penetration) while at the same time localizing their effect at the desired site of action (enhanced localization) (M. Mezei in "Liposomes as Drug Carriers" ed. G. Gregoriadis, John Wiley & Sons Ltd., New York 1988, pages 663–677).

Topical anesthetics are agents that reversibly block nerve conduction causing numbness and cessation of pain even after major stimuli. A topical analgesic agent is a substance which relieves pain without necessarily causing numbness, or which can relieve topical pain of a minor nature, but not of a great degree (Fed. Register 44, 69768–69866, 1979). These drugs are therefore used to treat or prevent pain. For operations of a peripheral or minor nature involving the skin, like removal of superficial skin lesions and plastic surgery, or intradermal allergen testing, split skin grafting, treatment of painful ulcers, venipuncture—the ideal way of anesthesia would be the topical application of local anesthetics.

The commercially available topical anesthetic preparations however, are not completely suitable for this purpose. Studies of Dalili and Adriani (Clin. Pharm. Ther., 12: 913–919, 1971) provided the first experimental evidence that manufactured preparations containing local anesthetics intended for use on the surface of the skin often lack a desired degree of efficacy. The preparations were tested on normal skin and on ultraviolet light burned skin for the ability to block itching and pricking induced by electrical stimulation. The only preparation judged sufficiently effective was one containing 20% benzocaine. But even the effect of this preparation disappeared within 60 seconds after it has been wiped off the test site. The authors indicated several possible reasons for the lack of efficacy, including the low concentration of the active ingredient, possible chemical change or interaction, for example, with other components and the penetration-preventing effect of the vehicle formulation used (J. Adriani and H. Dalili., Anesth., Analg. 50: 834–841, 1971).

At present, the most successful commercially available preparation for dermal anesthesia is a lidocaine-prilocaine cream, first reported by Juhlin et al. (Acta Derm Venereol. 59: 556–559, 1979). The cream consists of an emulsion containing 5% by weight of the eutectic mixture of lidocaine and prilocaine bases (EMLA) in water, thickened with Carbopol® (G. M. E. Ehrenstrom Reiz and SLA Reiz., Acta Anaesth. Scand., 26: 596–598, 1982). An application time of 60 minutes under occlusion achieves complete anesthesia to pinpricks, and the anesthetic effect lasts one to two hours (H. Evers et al., Br. J. Anaesth., 58: 997–1005, 1985).

In general, to achieve adequate local anesthesia of the skin using known preparations, a relatively excessive amount of drug, a prolonged application period or invasive methods are required. For adequate surgical anesthesia, the local anesthetic must be injected subcutaneously in order to reach sensory nerve endings lying in the dermis. When injecting a local anesthetic, pain is produced by the needle's penetration and by the deposition of the anesthetic solution. Distortion of the wound or performing the infiltration of large areas can also be problems in surgical cases (L. Juhlin, H. Evers, and F. Broberg., Acta Derm. Venereol., 60: 544–546, 1980).

In contrast to anesthetizing the skin, anesthesia of mucous membrane covered surfaces can be produced by topical application of local anesthetics quickly and easily. Unfortunately, rapid absorption of the local anesthetic through these surfaces into the circulatory system may reduce the duration of local anesthetic action, and since these drugs have low therapeutic ratios, may possibly cause systemic toxicity (J. A. Wildsmith, A. P. Rubin and D. B. Scott., Clin. Anaesth., 4: 527–537, 1986).

Thus, there is a continuing need in the art of local anesthesia for a preparation that is safe, yet effective on either unbroken skin, or on mucous membranes which provides a proper rate of drug permeation without discomfort or a risk of systemic reactions.

Local anesthetic agents previously have been encapsulated into liposomes. (Papahadjopoulos et al., Biochim. Biophys Acta, 394: 504–519, 1975). However, the liposome encapsulated local anesthetic was not used for producing local anesthesia or analgesia but rather was prepared as a way of studying the drug's mechanism of action, i.e. the interaction of the local anesthetic with the phospholipid bilayers, which in effect served as a model for a cellular membrane.

DESCRIPTION OF THE INVENTION

The present invention broadly relates to the use of liposomes for improving the effect on a mammal of topically applied preparations of local anesthetics and analgesics by enhancing the penetration (i.e. increasing cutaneous absorption) and localization (i.e. decreasing systemic absorption) of the anesthetic and analgesic agents.

The present invention may be used to provide local anesthetic and analgesic treatment for both human and veterinary purposes. Local anesthetics, as amphipathic agents, are good candidates for entrapment in the phospholipid bilayers of a liposome. Any anesthetic and analgesic agent or drug suitable for topical or local application can be used in the present invention including benzocaine, xylocaine, ketocaine, methyl salicylate, trolamine salicylate, lidocaine, prilocaine, tetracaine, pramoxine (tronothane) and dibucane. Tetracaine is a particularly useful agent because it is a potent topical anesthetic and owing to its relatively large hydrophobic moiety, it is easily encapsulated by phospholipid bilayers.

The amount of the anesthetic or analgesic agent or drug to be included in the liposomal preparation is not, per se, critical and can vary within wide limits depending inter alia on the particular agent, the intended application and the lipid used. Generally, the anesthetic or analgesic agent may be included in an amount of between about 0.1 to 10% by wt. of the liposomal preparation and more usually may be included in an amount of between 0.3 and 5.0% by wt.

Materials and procedures for forming liposomes are well-known to those skilled in the art and need not be described herein in detail. Reference is made to U.S. Pat. Nos. 4,485,054 and 4,761,288, which are hereby incorporated by reference, for a disclosure of preferred preparation techniques. Generally, the desired anesthetic or analgesic agent to be encapsulated is dissolved or dispersed in a lipid-containing organic solvent. Phospholipids are particularly useful, such as those selected

from the group consisting of phosphatidylchloines, lysophosphatidylchloines, phosphatidylserines, phosphatidylethanolamines, and phosphatidylinositols. Such phospholipids often are modified using for example, a modifying agent selected from the group consisting of cholesterols, stearylamines and tocopherols. The solvent then is evaporated, typically under a reduced pressure, to yield a thin lipid film containing the anesthetic or analgesic. Afterwards, the film is hydrated, with agitation, using a aqueous phase containing any desired electrolytes and lipid vesicles entrapping the anesthetic or analgesic are produced. As recognized by those skilled in the art, while certain materials and procedures may give better results with certain drugs, the use of particular materials and procedures are not narrowly critical and optimum conditions can be determined using routine testing. Although some of the liposome formulations acquire a gel-like consistency upon cooling to room temperature in the absence of any adjuvants, the present invention contemplates the use of conventional thickeners and gelling agents to provide a preparation having any desired consistency for topical application. Additionally, a preservative or antioxidant often will be added to the preparation.

A particular feature of the present invention is that a more pronounced cutaneous anesthetic or analgesic effect is obtained in the patient with a smaller amount of the active anesthetic or analgesic agent than compared with prior topical preparations. While not wishing to be bound to any theory, it is thought that the lipid vesicles facilitate transport of the anesthetic or analgesic drug through the stratum corneum barrier. Thus, preparations containing from 0.1 to 3.0% by wt. of the anesthetic or analgesic agent may be useful. The low drug concentration should permit its use as a safe and effective over-the-counter medication for painful skin disorders. In most cases, the anesthetic or analgesic agent comprises from about 5 to about 25% by wt. of the lipid, i.e. the phospholipid, neutral lipid, surfactant or similar material having the amphiphilic character needed to form the lipid vesicles.

The amount of the liposomal preparation to be applied to the patient can vary within wide limits depending inter alia an the particular site of application and the desired duration of effect. Generally, application of between about 0.005 to 0.5 g of liposomal preparation per square centimeter of surface to be anesthesized should be sufficient, with an amount of between 0.01 to 0.05 g/cm^2 being useful in many cases. Preferably, the liposomal preparations of the present invention are applied topically under occlusion to obtain enhanced effect.

The following examples are illustrative of the present invention and are not to be regarded as limitating. In the examples, several anesthetic agents, e.g. benzocaine, lidocaine, prilocaine, lidocaine-prilocaine eutectic mixtures, tetracaine and dibucaine, were encapsulated into liposomes using the procedure described in Mezei et al. U.S. Pat. No. 4,485,054. In order to increase the effective concentration of the encapsulated drug, e.g. with benzocaine, lidocaine and dibucane, where a reduced solubility restricted, to some extent, the upper concentration, the multiphase liposomal drug delivery system described and claimed in Mezei, U.S. Pat. No. 4,761,288 was utilized. Most of the time the base (and not the salt) of the anesthetic agent was used for preparing the liposomal product. It should be understood that all of the parts, percentages, and proportions referred to herein and in the appended claims are by weight unless otherwise indicated. The following examples demonstrate the formulas and the activity of selected anesthetic agents in liposome form versus ointment or cream form.

EXAMPLE 1

Formula:	
TetracaCine (base)	0.5 g
Soy phosphatidylcholine	7.0 g
Cholesterol	0.5 g
Stearic acid	0.7 g
Ethanol (95%)	10.0 ml
Propylene glycol	7.0 ml
Solution of sodium chloride (0.45 wt. %) and sodium bicarbonate (0.65 wt. %)	83.0 ml

The tetracaine base (pharmacopoeal grade), phosphatidylcholine (NC-95-H, American Lecithin Co., Atlanta, Georgia), cholesterol (Sigma Chem. Co.) and stearic acid (Fisher Scientific Co.) were dissolved in a chloroform:methanol (2:1 v/v) solvent solution in a pear-shaped flask, and small glass beads (100 g) were added. The solvent was evaporated to dryness in a rotary evaporator at 30° C. and under a reduced pressure, until a smooth, thin lipid film was obtained on the surface of the flask and the glass beads. The film then was hydrated with an aqueous phase prepared by mixing the aqueous solution of 0.65 wt. % $NaHCO_3$, and 0.45 wt. % NaCl, the ethanol and the propylene glycol, by shaking for 30 minutes in a Lab-Line Orbit Environ-Shaker at 55° C. The liposomes were separated from the glass beads by filtering the hydrated preparation through a Buchner funnel without using filter paper.

EXAMPLE 2

Formula:	
Lidocaine	2.0 g
Soy phosphatidylcholine	9.0 g
Tocopherol acetate	0.24 g
Hydroxypropylmethylcellulose	1.5 g
Aqueous solution of sodium chloride (0.45 wt. %) and sodium bicarbonate (0.65 wt. %)	100.0 ml

The lidocaine, soy phosphatidylcholine and tocopherol acetate were dissolved in a chloroform:methanol (2:1 v/v) solvent solution in a pear-shaped flask containing 100 g of small glass beads. The solvent was evaporated in a rotary evaporator at 30° C. and under reduced pressure until a thin, smooth film of the lipid and lidocaine was obtained on the surface of the glass beads and the wall of the flask. The resulting lipid film was hydrated at 55° C. using the aqueous sodium chloride and sodium bicarbonate solution in an environment shaker for 30 minutes. The hydroxypropylmethylcellulose was added to the preparation within 5 seconds after the lipid film and aqueous solution were mixed.

EXAMPLE 3

Dibucaine	1.0 g
Soy phosphatidylcholine	8.0 g
Tocopherol acetate	1.0 g
Hydroxypropylmethylcellulose	1.0 g
Tween ®-80	1.0 g

-continued

$CaCl_2$ solution 0.8 mM	100.0 ml

The method of preparation was substantially the same as that described above for Example 2; Tween ®-80 was added last to the liposomal product.

EXAMPLE 4

In a manner similar to the preceding examples, several other compositions were prepared using:

(a) different local anesthetic agents (e.g. benzocaine, prilocaine and a lidocaine-prilocaine eutectic mixture) with various concentrations of the active ingredient (i.e., 0.5 to 5 wt. %);
(b) phosphatidycholines of different origin and at various concentrations (i.e., 2–15 wt. %);
(c) cholesterol or tocopherol lipid vesicle modifiers in different concentrations (i.e., 0.5–5 wt. %);
(d) buffer solutions with various pH's and electrolyte contents;
(e) various viscosity inducing agents (e.g. methylcellulose, Carbopol ®, etc.) and
(f) various preservatives or antioxidant agents (e.g. benzoic acid, methyl and propyl paraben butylated hydroxyanisole (BHA), benzylalcohol, etc.);

The efficacy of the various local anesthetic agent preparations were tested in liposomal form against a commercial cream preparation or an ointment prepared using the same drug.

Evaluation of local anesthetic/analgesic activity

A protocol for human experiments was approved by the Ethics Committee for Human Research of the Faculty of Health Professions of Dalhousie University, Halifax, Canada. Healthy adult volunteers with no skin disorders or previous history of allergic sensitivity to local anesthetics were asked to participate in the study. Twelve subjects in each experimental group having ages ranging from 25 to 60 years were investigated.

Example A: Tetracaine (0.5 wt. %) Liposomal Preparation

Liposomal preparation containing about 0.5 wt. % tetracaine base (formula as Example No. 1) and Pontocaine ® cream (tetracaine hydrochloride cream U.S.P., equivalent to 1% tetracaine base, manufactured by Winthrop Laboratories Aurora, Ontario, Lot No. 120 BL) were compared. A 0.2 ml volume of the liposomal preparation was applied to a 10 cm^2 area marked by ink on the volar surface of one forearm of each of the volunteers and covered with Blenderm ® tape (3M Co., St. Paul, Minnesota) to form an occlusive dressing. The same amount of Pontocaine ® cream was applied to the other arm of each volunteer in the same manner. The samples of the liposomal preparation and the commercial preparation were randomly numbered, and the number of applied preparations recorded for each subject. The identity of the preparations was not known for the subjects or for the evaluator so as to maintain the "double blind" study design.

The samples were applied for 30 minutes in the first group of volunteers and for 60 minutes in the second group. After each of these time intervals the covering tape was removed and the tested area wiped dry with a tissue paper. Onset and duration of anesthesia at the test sites were tested using the pin-prick technique, described in detail by Lubens et al. (Am. J. Dis. Child., 128: 192–194, 1974). At each test period, each skin test area was pricked ten times using a relatively blunt sterile needle, to allow each subject to discriminate between the perception of touch and pain. Ten painless pricks at the time of the test was indicative of complete anesthesia. Sensitivity for each subject was confirmed by pin-pricking near to the test site areas before applying the samples to be tested. Testing score indexes were obtained from each of the volunteers by noting the number of painfree pin-pricks out of the 10 in both test areas. Testing was done immediately after the preparations had been removed from the test site, and then at 30 min., 1 h, 2 h, and 4 h afterwards. Results are reported in Tables 1 and 2.

As shown by the results in Tables 1 and 2 the liposome preparation containing 0.5% tetracaine base was effective in producing dermal anesthesia. After the onset of anesthesia the perception of pain was greatly reduced, although the pressure could be felt. The perception of cold also was observed to disappear at the "numb" test sites (by testing with a cold metal rod). Sensitivity of nerve fibers conveying the sensations of pain, cold, warmth, touch and deep pressure to local anesthetic action is differential. This is correlated with the fiber diameter, that increases from the fibers conveying the sensation of pain to those conveying deep pressure. Pain fibers are the first to be blocked, followed by sensations of cold, warmth, touch and deep pressure. Apparently, the absorbed doses in these tests were high enough only to block the pain and cold fibers, having no or little effect on touch or pressure sensations.

The results also show that the duration of application influences the intensity and duration of the anesthetic effect. On removal of the preparation after 30 minutes of application, the anesthesia was less pronounced, than after a one hour period of application. In both cases, the anesthesia effect improved with time after initial application. Since the onset of anesthetic action is not necessarily immediate, the preparation can be dispensed for administration suitably in advance of any painful procedure. A maximum in anesthetic effect was reached in both the 30 minutes and 1 hour application time groups about two hours after removal of the preparation at an average painless score of 8.25 and 9.5 respectively. Approximately, this level of anesthesia was maintained until the end of the experiments. Tests were conducted only up to 4 hours after removal of the preparations, but the anesthesia provided by the present invention was reported by the volunteers to persist longer, from 5 to 8 hours, depending on the application time.

Considerable inter-individual variations were observed in the onset time of action. Painless scores in the 30 minutes and 1 hour period of application time groups at the time of removal were, respectively, at or above 7 in 25% and 50% of all the subjects tested (N=12). Pontocaine cream, the control preparation, was found to be relatively ineffective over the entire test period, in agreement with findings of Dalili and Adriani (Cin. Pharm. Ther., 12: 913–919, 1971).

Statistical analysis of the data by paired t-tests indicated a statistically highly significant difference in favor of the liposomal tetracaine over the commercial preparation (See Tables 1 and 2).

Example B: Lidocane (2 wt. %) Liposomal Preparation

Liposomes with about 2 wt. % lidocaine (preparation as Example No. 2) were compared to a placebo, which consisted of "empty" liposomes with the same composi-

tion as that of the active preparation but without lidocaine. A comparison of the 2 wt. % lidocaine liposomes also was carried out with a control, which contained 2 wt. % lidocaine incorporated in Dermabase ® as the vehicle. In both groups, the length of application of liposomal and control preparations was one hour. The procedures of Example A were repeated and the results are reported in Tables 3 and 4.

The anesthetic effect of the 2 wt. % lidocaine liposomes compared to the placebo, as measured by the painless scores, is shown in Table 3. Similarly to the tetracaine liposomal preparation, lidocaine encapsulated in liposomes produced anesthesia in the intact skin after topical application.

TABLE 1

Mean painless scores at different times of observation after an initial 30 minutes application period under occlusion of 0.5% tetracaine liposome preparation and Pontocaine ® cream.
Number of volunteers = 12
Statistical analysis by paired t-tests

	Lipsome preparaton		Pontocaine ® cream		
Time	Mean	SD	Mean	SD	P
at removal	2.75	3.25	0.25	1.73	0.0644
30 Min	5.50	3.94	1.08	1.98	0.0117
1 hour	6.75	3.28	1.08	1.68	<0.0001
2 hours	8.25	2.45	1.08	1.31	<0.0001
4 hours	8.33	2.31	0.25	0.62	<0.0001

TABLE 2

Mean painless scores at different times of observation after an initial 1 hour application period under occlusion of 0.5% tetracaine liposome preparation and Pontocaine ® cream
Number of volunteers = 12
Statistical analysis by paired t-tests

	Lipsome preparation		Pontocaine ® cream		
Time	Mean	SD	Mean	SD	P
at removal	6.25	3.65	0.08	0.29	<0.0001
30 min	8.08	2.27	0.41	0.99	<0.0001
1 hour	8.83	1.47	0.25	0.62	<0.0001
2 hours	9.50	0.67	0.33	1.15	<0.0001
4 hours	8.75	1.48	0.16	0.57	<0.0001

The pain and cold sensations were greatly reduced, but not the perception of pressure. The intensity of the anesthetic effect again continued to increase after the removal of the preparation, and reached its maximum value one hour later. The differences between the placebo and the liposome-encapsulated lidocaine preparation were statistically significant at every time point (Table 3). Similar results to the placebo experiment and to Example A were obtained when liposomal lidocaine was compared to lidocaine in a Dermabase ® vehicle (see Table 4).

Example C: Other Preparations

Table 5 presents and compares the liposomal tetracaine preparation of the present invention with several other anesthestic preparations designed for topical application.

Thus, while certain specific embodiments of the invention have been described with particularity herein, it will be recognized that various modifications thereof will occur to those skilled in the art and it is to be understood that such modifications and variations are to be included within the purview of this application and the spirit and scope of the appended claims.

TABLE 3

Mean painless scores at different times of observation after an initial 1 hour application period under occlusion of 2% lidocaine liposome preparation and placebo
Number of volunteers = 12
Statistical analysis by paired t-tests

	Lipsome preparation		Placebo		
Time	Mean	SD	Mean	SD	P
at removal	4.08	4.42	1.08	1.51	0.0337
30 min	6.08	4.14	1.33	1.92	0.0040
1 hour	7.25	3.86	2.08	2.23	0.0040
2 hours	6.16	3.35	1.58	2.81	0.0062
3 hours	5.33	3.17	1.16	2.04	0.0042

TABLE 4

Mean painless scores at different times of observation after an initial 1 hour application period under occlusion of 2% lidocaine liposome preparation and 2% lidocaine in Dermabase ® (control)
Number of volunteers = 5
Statistical analysis by paired t-tests

	Lipsome preparation		Dermabase ® (control)		
Time	Mean	SD	Mean	SD	P
at removal	6.2	3.56	1.8	2.49	0.103
30 min	7.4	3.71	2.6	1.67	0.018
1 hour	9.8	0.45	3.6	0.89	<0.001
2 hours	8.6	1.14	3.2	1.30	<0.001
3 hours	4.6	3.13	2.2	2.17	0.051

TABLE 5

Comparison of liposomal tetracaine preparation with other formulations for topical anesthesia

Reference	Drug	Vehicle	Onset time	Duration	Dosage	Side Effect
Monash, S. Arch. Dermatol. 76:752–56, 1957.	5% tetracaine	ointment	1.5 h	3.5 h	additional ointment hourly	
Lubens, H. M. Sanker, J. F. Ann, Allerg. 22:37–41, 1964.	30% xylocaine	"acid mantle cream"	2 h—4 h—(application)	0.5 h 3 h	"liberal amount"	
Brechner, V. L. et al. Ann. N.Y. Acad. Sci. 141:524–31, 1967.	5–33% tetracaine	dimethyl sulfoxide (DMSO)	0.5 h	3 h	1 ml to 5 × 5 cm area	pruritis hypersensitivity
Ohlsen, L. Englesson, S. Brit. J. Anaesth. 52:413–16, 1980.	10% ketocaine	isopropranol glycerol water	1–10 h	several hours	5.3 ml to 8 × 10 cm area	erythema oedema
Evers. H. et al. Brit J. Anaesth. 58:997–1005, 1985.	5% lidocaine-prilocaine (EMLA)	oil in water emulsion	1 h	1 h	1 g to 6.25 cm^2 area	
This Invention	0.5% tetracaine	liposome	0.5–1 h	at least 4 h	0.2 ml to 3 × 3	

TABLE 5-continued

Comparison of liposomal tetracaine preparation with other formulations for topical anesthesia						
Reference	Drug	Vehicle	Onset time	Duration	Dosage	Side Effect
		preparation			cm area	

We claim:

1. A method for providing local anesthesia or analgesia to a mammal which comprises topically applying a composition to said mammal in an amount of between about 0.005 to 0.5 g/cm^2 of surface to be anesthesized, said composition containing an anesthetic or analgesic agent selected from the group consisting of benzocaine, xylocaine, ketocaine, methyl salicylate, trolamine salicylate, lidocaine, prilocaine, tetracaine, pramoxine and dibucaine, encapsulated within lipid vesicles in an amount of between about 0.1 to 10% by wt. of said composition.

2. The method of claim 1 in which the composition contains multilamellar lipid vesicles.

3. The method of claim 1 wherein the lipid vesicles comprise unilamellar lipid vesicles.

4. The method of claim 1 wherein the lipid vesicles are multivesicular.

5. The method of claim 1 wherein said lipid vesicles are prepared using a phospholipid.

6. The method of claim 5 wherein the phospholipid is selected from the group consisting of phosphatidylchloines, lysophosphatidylchloines, phosphatidylserines, phosphatidylethanolamines, and phosphatidylinositols.

7. The method of claim 6 wherein the phospholipid is provided in admixture with a modifying agent selected from the group consisting of cholesterols, stearylamines and tocopherols.

8. The method of claim 7 wherein the anesthestic or analgesic agent is selected from the group consisting of benzocaine, xylocaine, ketocaine, lidocaine, prilocaine, tetracaine and dibucaine.

9. The method of claim 8 wherein the composition contains said anesthestic or analgesic agent in an amount between about 0.3% and 5.0% by weight.

10. A pharmaceutical composition comprising lipid vesicles having a topical anesthetic or analgesic agent selected from the group consisting of benzocane, xylocaine, ketocaine, methyl salicylate, trolamine salicylate, lidocaine, prilocaine, tetracaine and pramoxine, encapsulated therein in an amount of between about 0.1 to 10% by wt. of said composition.

11. The composition of claim 10 wherein the lipid vesicles are multilamellar.

12. The composition of claim 10 wherein the lipid vesicles are unilamellar.

13. The composition of claim 10 wherein the lipid vesicles are multivesicular.

14. A method for providing local anesthesia or analgesia to a mammal which comprises topically applying to said mammal a composition containing phospholipid vesicles encapsulating 0.1 to 10% by wt. of an anesthetic or analgesic agent, wherein said composition is applied in an amount between about 0.005 to 0.5 g/cm^2 of surface to be anesthesized.

* * * * *

Exhibit 5

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1	4,937,078	283	465	0	07/236,724	06/26/90	08/26/88	04	YES	PAID

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1	4,937,078	284	1025	0	07/236,724	06/26/90	08/26/88	08	YES	PAID

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1	4,937,078	285	1550	065	07/236,724	06/26/90	08/26/88	12	YES	PAID

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Director of Product Development
Blue Ridge Pharmaceuticals, Inc.
4249-105 Piedmont Parkway
Greensboro, NC 27410

Dear Dr. Lynn:

We refer to your submissions dated September 8, 1998 (E0003), and December 4, 1998 (G0008), to your Investigational New Animal Drug (INAD) file for diclofenac 1% suspension. The drug is a nonsteroidal anti-inflammatory proposed for topical use for the management of pain and inflammation in horses.

The E0003 submission contained protocols for a clinical field trial and a target animal safety study for our review.

The G0008 submission contained a request for categorical exclusion from the requirement to prepare an Environmental Assessment (EA). We have completed our review of the submission and agree that a categorical exclusion under 21 CFR 25.33(e) is appropriate for the INAD. We acknowledge that to your knowledge, no extraordinary circumstances exist which may significantly affect the human environment as discussed under 21 CFR 25.21. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Comments concerning Study Number BRP-DEQ-02, "Clinical Field Trial to Evaluate the Safety and Efficacy of Topically Applied 1% Diclofenac Liposomal Suspension for the Relief of Lameness in Horses":

1. In several telephone conversations with Dr. Ellen Buck, most recently on December 3, 1998, we have discussed substantial modifications to the field trial protocol that you are considering. You mentioned that you may employ an approved positive control in lieu of placebo control as currently written.

   In studies using an approved positive control, the test article should perform at least as well as the positive control. Please note that if the positive control is more effective than the test article, the study would not be considered as supportive of the test article's effectiveness. Also, it is generally easier to show effectiveness compared to placebo than to show equivalence to a positive control.

Blinding of all personnel involved in evaluation of the product's effectiveness should be maintained in positively controlled studies, as in placebo controlled studies. This may be more difficult if the dosage form of the test article and positive control are not similar.

2. The primary variable of interest to CVM will be the veterinarian's assessment of lameness score. Range of motion and pain on manipulation are not reliable indicators of pain in horses. Most horses, even those with severe lameness, will exhibit no loss of range of motion. Some horses with pronounced loss of range of motion will be perfectly sound. A severe loss of range of motion would generally be 25%. Similarly, many lame horses will not show any signs of pain on passive flexion of the affected joint. Owners' evaluations will not be considered in our analysis of diclofenac's effectiveness.

3. The protocol includes several interim lameness exams. Our effectiveness evaluation will be based on the difference between initial and final lameness evaluations. If improvement is noted only during interim evaluations, it will not be considered evidence of the product's effectiveness.

4. The lameness scoring scale currently proposed is somewhat vague. Instead, we recommend that you use the generally recognized American Association of Equine Practitioners (AAEP) lameness scoring scale.

5. A sample size of 25 horses per group may be too small to detect effects of interest in this protocol. For example, we might expect around 20% of animals in the placebo group to show improvement after 7 days. With 25 horses/group, the underlying percentage improvement of horses in the treatment group would have to be approximately 55% or greater for a statistical test to detect a significant difference. With 50 horses/group, this underlying percentage improvement drops to approximately 45% or greater.

6. Please provide clarification about how data from animals withdrawn from the study due to lack of effectiveness will be evaluated. We recommend that an animal that is withdrawn due to lack of effectiveness be scored as "Did not improve". The number of animals that were withdrawn due to lack of effectiveness can also be compared statistically between the two groups.

7. You have proposed a non-parametric test to compare the two groups. This test is appropriate for tests done cross-sectionally at each time period. However, the test cannot incorporate information about the animal's condition at baseline. We

recommend that the percentage of animals showing improvement by at least one level of the lameness scale between Day 0 and Day 7 be considered primary and be analyzed by an exact test procedure. The animals that were withdrawn due to lack of effectiveness should be included in this analysis.

Comments concerning Study Number BRP-DEQ-04, "Target Animal Safety Study of 1% Diclofenac Liposomal Suspension Applied Topically to Horses – A 28 Day Study":

1. A review of available publications concerning the use of topical diclofenac in humans suggests that the drug is absorbed systemically, and that it is capable of causing adverse reactions typical of many NSAIDs, most notably gastric irritation. Therefore, we recommend modifying the Target Animal Safety study to better identify the occurrence, if any, of systemic adverse reactions that could develop following overdose, such as might occur following overzealous application of the product by a horse owner.

   In the protocol as written, all applications of drug will be to a single joint. The advantage of this technique is that it may maximize signs of dermal or local irritation. However, we believe applying portions of the dose to more than one joint, thereby covering more surface area with the drug, may result in increased absorption of diclofenac, and give a better indication of its systemic effects following overdose. In real-life overdose situations, one would anticipate owners both applying excessive amounts of drug to a single joint, and applying drug to multiple joints.

   We also recommend including periodic endoscopic evaluation of the stomach, preferably pretreatment and at least once mid study, since this is the only definitive method for diagnosing gastric erosion or ulceration.

2. The protocol states that the study will be conducted for 28 days. The Target Animal Safety Study should be conducted for at least 3X the intended duration of treatment. In our conference on June 30, 1998, you stated your intention to pursue a 14 day treatment duration. For a labeled treatment duration of 14 days, safety studies should be conducted for a minimum of 42 days.

3. The protocol includes 1X, 3X, and 5X multiples of the intended dose. A 10X acute toxicity group should also be evaluated, for at least 1X the intended duration of treatment. You may either include a 10X group in this study, or conduct a separate acute toxicity study. In order to minimize the number of horses sacrificed, you may prefer to incorporate the 10X group into this study, and conduct complete necropsy and histopathologic examination on the 10X group. You should sacrifice and

evaluate all horses in a given treatment group (for example, all 10X horses and all control horses), rather than a limited sample of horses within a treatment group.

Please note that the intent of Target Animal Safety Studies is not only to characterize the types of toxicities that may result from treatment, but also to identify at what dose level any adverse effects begin to manifest. If you elect to sacrifice only the highest treatment dose group, and lesions are found on gross examination or on histopathology, it would be necessary to sacrifice lower dose treatment groups in order to better identify at what dose level toxicity begins. If alterations are not apparent until histopathologic evaluation, and the remaining animals have been off treatment for some time, it may be necessary to repeat the study, at a minimum with the lower dose groups.

4. In addition to the tissue samples to be evaluated outlined in the protocol, a more comprehensive evaluation of the test site should also be conducted. This should include complete histopathology of the joint and related structures (synovium, cartilage, subchondral bone) over which the topical product is applied. A synovial fluid analysis should also be conducted. If all applications are to be made on a single joint, examination of the contralateral untreated joint from the same animal may afford the most meaningful comparison when looking for localized adverse effects.

5. Page 9 of the protocol states "Supplemental feed consumption will be measured and recorded weekly during the study." We are unclear what is meant by "supplemental feed consumption." We agree that feed consumption should be measured, at least at intervals, during the study. Loss of appetite secondary to gastric irritation is a potential adverse reaction to NSAIDs.

6. Blinding of the study should be maintained to reduce the risk of bias in interpreting the results. The frequency of application of diclofenac will make apparent which horses belong to which dosage group. Therefore, the individual(s) making antemortem and postmortem evaluations should not be involved in application of the product, or otherwise be aware of treatment group assignment. The protocol should state how blinding of the study will be maintained.

7. The untreated control horses should receive sham treatment, such as application of saline solution to a specified joint, or massage of the skin over a selected joint, to mimic the handling and manipulation of the treated animals. Such treatment would help identify which lesions that appear on necropsy, if any, are due to handling stress, as opposed to actual treatment effects.

8. To your proposed group pair-wise comparisons and repeated measures ANOVA, we recommend that you add an inspection of the interaction of gender with the other fixed effects. Because the number of animals in each gender by treatment group is small (3), you may want to inspect the interaction of gender with other fixed effects graphically rather than analytically. The decision of whether or not to pool data across gender should be on the basis of this inspection.

   Again, because the number of animals in each gender by treatment group is small, you may consider inspecting the model residuals graphically rather than conducting a formal test for heteroscedastic error to motivate the use of variance stabilizing transformations.

Future correspondence regarding these submissions to your INAD file should be identified by the submissions' correspondence date and our file numbers, INAD 10294 E0003, G0008, and submitted directly to the Document Control Unit (HFV-199).

If you have any questions or if we can be of further assistance, please contact Dr. Linda Wilmot, Leader, Equine and Antimicrobial Drugs Team. The telephone number is (301) 827-7540.

Sincerely yours,

Melanie R. Berson, DVM

Melanie R. Berson, DVM
Director
Division of Therapeutic Drugs
for Non-Food Animals
New Animal Drug Evaluation
Center for Veterinary Medicine

Exhibit 7

December 27, 2000

IDEXX
Blue Ridge Pharmaceuticals
4249-105 Piedmont Parkway
Greensboro, NC 27410
Office: 336-852-4040
Fax: 336-852-3540

Dr. Melanie R. Berson
Director, Division of Therapeutic Drugs for Non-Food Animals
HFV-110, Room N301
FDA, Center for Veterinary Medicine
7500 Standish Place
Rockville, MD 20855

Dear Dr. Berson:

Re: Diclofenac Liposomal Cream- New Animal Drug Application (NADA)

Enclosed please find our New Animal Drug Application (NADA) for Diclofenac Liposomal Cream. The data for this NADA were gathered under INAD number 10-294.

We have addressed all the issues raised in your review letters. The CVM comments and our responses are contained in the applicable sections of the NADA.

The following technical sections are included in this submission:

Technical Section	Studies/Information
Identification	Section 1 – Identification
Table of Contents and Summary	Section 2 - Table of Contents and Summary
Labeling	Section 3 – Labeling
Components and Composition	Section 4 – Components and Composition
Manufacturing Methods and Controls	Section 5 – Manufacturing Methods, Facilities and Controls
Samples	Section 6 – Samples
Analytical Methods for Residues	Section 7 - Analytical Methods for Residues
Evidence to Establish Safety and Effectiveness	Section 8 - Evidence to Establish Safety and Effectiveness
Good Laboratory Practice Compliance	Section 9 - Good Laboratory Practice Compliance
Environmental Assessment	Section 10 – Environmental Assessment
Freedom of Information Summary	Section 11 - Freedom of Information Summary
Other	Section 12 – Confidentiality of Data and Information in a New Drug Application

Enclosed please find two (2) volumes, for your review and comment. Three (3) copies of each volume are enclosed and are labeled as follows:

Volume ___ of 2

SURPASS™
(Diclofenac 1% Liposomal Cream)

Complete NADA

NADA:	_____
Date:	December 27, 2000
Dosage Form:	1% Liposomal Cream
Route:	Topical
Species:	Equine
Indications:	Relief of lameness in horses.
Contents:	Sections 1-12 (Complete NADA)
Sponsor:	Blue Ridge Pharmaceuticals, Inc. 4249-105 Piedmont Parkway Greensboro, NC 27410

In addition to the paper documents, we have enclosed a compact disc that contains computer files that support Sections 3, 5, 8 and 11 of this NADA. We also enclose four video-tapes of equine gastroscopy and necropsy that support Section 8a of the application.

Thank you for your continued cooperation. If you have any questions or comments, please call me at 336-834-6506.

Sincerely,

Randy C. Lynn, DVM, MS, DACVCP
Director of Product Development

Enclosures

CC: FDA Atlanta Office

Exhibit 8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NADA 141-186

January 2, 2001

Randy C. Lynn, DVM, MS, DACVCP
Director of Product Development
Blue Ridge Pharmaceuticals
4249-105 Piedmont Parkway
Greensboro, NC 27410

Dear Dr. Lynn:

We acknowledge receipt of your submission dated December 27, 2000, which pertains to the establishment of a New Animal Drug Application for use of diclofenac liposomal cream for control of lameness in horses.

Your submission has been assigned **NADA number 141-186.** Please refer to this number when submitting any future correspondence pertaining to this application.

The application is being forwarded to the appropriate division for review.

This is not an approval letter.

Sincerely,

Carol Goolsby
Technical Information Specialist
Center for Veterinary Medicine
HFV-199

Exhibit 9

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
AGENCY: Food and Drug Administration.
21 CFR Part 60
Patent Term Restoration Regulations

[Docket No. 89N-0169]
RIN 0905-AD16

56 FR 5784

February 13, 1991

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its patent term restoration regulations to implement the patent term restoration provisions of the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100-670) (the Animal Drug Act). Current FDA regulations address patent term restoration, also known as patent term extension, for certain patents claiming human drug products (including biologics and antibiotics), medical devices, food additives, and color additives subject to regulation under the Federal Food, Drug, and Cosmetic Act (the act) and the Public Health Service Act (PHSA). The proposed rule would expand the scope of the regulations to include patents claiming new animal drug products.

DATES: Comments by April 15, 1991. The agency proposes that any final rule that may be issued based upon this proposal shall become effective 30 days after the date of publication of the final rule in the Federal Register.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.
FOR FURTHER INFORMATION CONTACT: Nancy E. Pirt, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

TEXT: SUPPLEMENTARY INFORMATION:

I. Introduction

On November 16, 1988, the President signed into law the Generic Animal Drug and Patent Term Restoration Act (the Animal Drug Act). Title I of the Animal Drug Act amended the Federal Food, Drug, and Cosmetic Act (the act) *(21 U.S.C. 301*-392) to authorize abbreviated new animal drug applications (ANADA's). Title II of the Animal Drug Act amended the patent term restoration provisions at *35 U.S.C. 156* to include patents claiming certain animal drug products.

A U.S. patent is effective for 17 years from the date of issuance. A patent does not permit an inventor to make, use, or sell his or here invention; instead, the patent enables the inventor to prevent others from making, selling, or using the patented invention. Federal statutes and regulations require some products, such as drugs and medical devices, to be approved by the Federal Government before they may be marketed. For these products, patent time may be lost awaiting that approval.

In September 1984, the Drug Price Competition and Patent Term Restoration Act (Pub. L. 98-417) (the PTR Act) became law. Title II of the PTR Act provided patent term restoration to patent holders whose patents claimed human

drug products (including biologics and antibiotics), medical devices, food additives, or color additives. Basically, patent holders could add as much as 5 years to their patent terms to compensate for the time elapsed during regulatory review. In no case, however, could the effective patent life for the product (the time between marketing approval and the expiration of the patent term) be extended to exceed 14 years.

The PTR Act's provisions, however, did not encompass animal drug products. Consequently, several bills were introduced during the 99th and 100th Congresses to extend patent term restoration to animal drug products. The Animal Drug Act (Pub. L. 100-670) achieved this goal in November 1988 by amending the existing patent term restoration provisions at *35 U.S.C. 156* to include animal drug products and biologics.

FDA, the U.S. Patent and Trademark Office (PTO), and the U.S. Department of Agriculture (USDA) share responsibility for implementing the patent term restoration provisions. PTO has primary responsibility over the program. PTO accepts applications, determines whether a patent is eligible for patent term extension, and, if appropriate, issues a certificate of extension. FDA assists PTO in its eligibility determination for products regulated under the act and determines the patented product's regulatory review period, which is the basis of any patent term extension. If necessary, FDA also hold informal hearings to determine whether the marketing applicant acted with due diligence during the review period.

USDA has patent term restoration authority similar to FDA's. USDA determines regulatory review periods relating to products approved under the Virus-Serum-Toxin Act and is authorized to hold hearings to determine whether applicants acted with due diligence.

The proposed regulation set forth in this document expands the scope of the existing patent term restoration regulations at 21 CFR part 60 to encompass animal drug products regulated under the act. The proposal also makes several technical and editorial changes to the existing regulations.

II. Provisions of This Proposal

A. Scope

FDA proposes to amend 21 CFR 60.1(a) to add animal drug products to the list of products for which patent term restoration is available. The proposal also adds to the text the "Public Health Service Act" *(42 U.S.C. 262)* as an additional regulatory authority.

B. Definitions

The agency proposes to amend several definitions in 21 CFR 60.3 to include animal drug products.

Active ingredient (21 CFR 60.3(b)(2)) would be redefined as any component that is intended to "furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or of animals."

Clinical investigation or study (21 CFR 60.3(b)(5)) would be amended to remove the adjective "human" from the existing regulation. This change is necessary since clinical studies on animal drug products do not involve human subjects.

The definitions of marketing applicant at 21 CFR 60.3(b)(11) and Marketing applications at 21 CFR 60.3(b)(12) would be revised to include applications for FDA premarket approval submitted under section 512 of the act *(21 U.S.C. 360b)*.

The definition of "product" at 21 CFR 60.3(b)(14) would be revised to include animal drug products.

The proposed rule also contains a new § 60.3(b)(16) defining "animal drug product." The definition excludes products that are primarily manufactured using biotechnology, as provided in Public Law 100-670.

C. Eligibility Assistance

FDA proposes to amend 21 CFR 60.10 by adding new paragraph (a)(3) to provide that, upon written request from PTO, the agency will assist PTO in determining whether a patent related to an animal drug product is eligible for commercial marketing or use of the animal drug product is the first permitted commercial marketing or use of the drug under the provision of law under which the regulatory review period occurred. If permission was for commercial marketing or use in food-producing animals, FDA will notify PTO whether the permission for use in food-producing animals is the first permitted commercial marketing or use of the drug for administration to a food-producing animal under the provision of law under which such regulatory review period occurred. This proposal implement *35 U.S.C. 156*(a)(5)(C), which enables patent holders to extend the term of a patent whose claims pertain to a food-producing animal use, notwithstanding previous approval of animal drug products containing the same active ingredient for use in nonfood-producing animals, provided that the patent was not extended on the basis of a use in nonfood-producing animals. This proposal also would amend 21 CFR 60.10(a)(3) by redesignating it as 21 CFR 60.10(a)(4) and revising it to indicate that the application for patent extension for an animal drug is to be filed within 60 days of the first approval for marketing or use, or of the first approval by FDA for administration to food-producing animals, whichever is applicable, and to accommodate the proposed amendment discussed above.

FDA also proposes in 21 CFR 60.10 to amend paragraph (a)(2) to emphasize its applicability to human drug products, food additives, color additives, and medical devices, and to redesignate existing paragraph (a)(4) as new paragraph (a)(5) to accomodate the proposed amendments discussed above.

D. Regulatory Review Period Determinations

Proposed paragraphs (d) and (e) in 21 CFR 60.22 incorporate the statutory definition *(35 U.S.C. 156*(g)(4)) of an animal drug product's regulatory review period. The regulatory review period consists of the sum of the lengths of a testing phase and an approval phase. Proposed § 60.22(d) defines the testing phase for an animal drug as the period beginning on the date when the marketing applicant began a major health or environmental effects test or the effective date for a notice of claimed investigational exemption for a new animal drug (INAD), whichever is earlier, and ending when the marketing applicant initially submitted a new animal drug application (**NADA)** . The approval phase is the time between initial submission of the **NADA** and its approval.

FDA believes that the date on which the agency acknowledges the filing of an INAD should constitute the "effective date" for an INAD. The date on which a **NADA** will be considered to have been initially submitted with respect to the animal drug product under section 512(b) of the act will be the date of FDA's official acknowledgment letter assigning a number to the **NADA.** FDA intends to adhere to current agency policy regarding **NADA** approval dates. In brief, the approval date for a **NADA** depends upon the type of new animal drug product. If the product is a dosage form drug, i.e., tablet, capsule, or soluble powder, or a Category I Type A medicated article that is not to be mixed with a Category II Type A medicated article, the **NADA** is approved when FDA sends a letter to the marketing applicant notifying it of the approval. If the product is a Category II Type A medicated article, approval is effective upon publication of the notice of approval in the Federal Register.

The regulatory review period for animal drugs, like that for food and color additives, can begin when a major health or environmental effects test is begun. 21 CFR 60.22(b)(1) defines a "major health or environmental effects test". Rather than repeat this definition in a separate section corresponding to an animal drug product's regulatory review period, FDA proposes to transfer the existing definition to a new § 60.22(e) which would be applicable to animal drug products as well as food and color additives.

FDA also proposes in § 60.22 to redesignate existing paragraph (d) as new paragraph (f) to accommodate the proposed amendments discussed above. FDA further proposes to add a sentence to the end of new paragraph (f) to clarify the meaning of the term "regulatory review period" for animal drugs.

III. Economic Assessment

The agency has considered the economic impact of this rule and the relationship of its requirements to Public Law 100-670. The patent term restoration provisions in Public Law 100-670 will result in economic consequences for affected patent holders and their competitors.

The agency concludes, however, that this rule is not a "major rule" as defined by Executive Order 12291 and does not require a regulatory impact analysis. Similarly, the agency certifies that this rule will not have a significant economic impact on a substantial number of small entities, and therefore does not require a regulatory flexibility analysis under the Regulatory Flexibility Act of 1980 *(5 U.S.C. 601*-611, Pub. L. 96-354).

IV. Environmental Impact

The agency has determined that under 21 CFR 25.24(a)(8), this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Paperwork Reduction Act of 1980

This proposed rule does not add any information collection requirements to 21 CFR part 60 although, pursuant to law, it does expand the scope of eligible products.

VI. Request for Comments

Interested persons may, on or before April 15, 1991, submit to the Dockets Management Branch (address above), written comments on this recommendation. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the name of the device and the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday though Friday.

List of Subjects in 21 CFR Part 60

Administrative practice and procedure, Drug, Food additives, Inventions and patents, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, the Drug Price Competition and Patent Term Restoration Act, and the Generic Animal Drug and Patent Term Restoration Act, it is proposed that 21 CFR part 60 be amended as follows:

PART 60 -- PATENT TERM RESTORATION

1. The authority citation for 21 CFR part 60 is revised to read as follows:

Authority: Secs. 409, 505, 507, 515, 520, 701, 706 of the Federal Food, Drug, and Cosmetic Act *(21 U.S.C. 348,* 355, 357, 360e, 360j, 371, 376); sec. 351 of the Public Health Service Act *(42 U.S.C. 262); 35 U.S.C. 156.*

2. Section 60.1 is amended in the introductory text of paragraph (a) by revising the second sentence to read as follows:

§ 60.1 Scope.

(a) * * * Patent term restoration is available for certain patents related to drug products (as defined in *35 U.S.C. 156*(f)(2)), and to medical devices, food additives, or color additives subject to regulation under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act. * * *

* * * * *

3. Section 60.3 is amended by revising the first sentence in paragraph (b)(2), the first sentence in paragraph (b)(5), and paragraphs (b)(11) (ii) and (iii), by adding new paragraph (b)(11) (iv), by revising paragraphs (b)(12) (ii) and (iii), by adding new paragraph (b)(12)(iv), by revising paragraph (b)(14), and by adding new paragraph (b)(16), to read as follows:

§ 60.3 Definitions.

* * * * *

(b) * * *

(2) Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or of animals. * * *

* * * * *

(5) Clinical investigation or study means any experiment that involves a test article and one or more subjects and that is either subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), 512(j), or 520(g) of the Federal Food, Drug, and Cosmetic Act, or is not subject to the requirements for prior submission to FDA under those sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be submitted later to, or held for inspection by, FDA as part of an application for a research or marketing permit. * * *

* * * * *

(11) * * *

(ii) Section 515 of the Act (medical devices);

(iii) Section 409 or 706 of the Act (food and color additives); or

(iv) Section 512 of the Act (animal drug products).

(12) * * *

(ii) Medical devices submitted under section 515 of the Act;

(iii) Food and color additives submitted under section 409 or 706 of the Act; or

(iv) Animal drug products submitted under section 512 of the Act.

* * * * *

(14) Product means a human drug product, animal drug product, medical device, food additive, or color additive, as those terms are defined in this section.

* * * * *

(16) Animal drug product means the active ingredient of a new animal drug (as that term is used in the Act) that is not primarily manufactured using recombinant deoxyribonucleic acid (DNA), recombinant ribonucleic acid (RNA), hybidoma technology, or other processes involving site-specific genetic manipulation techniques, including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

3. Section 60.10 is revised to read as follows:

§ 60.10 FDA assistance on eligibility.

(a) Upon written request from PTO, FDA will assist PTO in determining whether a patent related to a product is eligible for patent term restoration as follows:

(1) Verifying whether the product was subject to a regulatory review period before its commercial marketing or use;

(2) For human drug products, food additives, color additives, and medical devices, determining whether the permission for commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use of the product either:

(i) Under the provision of law under which the regulatory review period occurred; or

(ii) Under the process claimed in the patent when the patent claims a method of manufacturing the product that primarily uses recombinant deoxyribonucleic acid (DNA) technology in the manufacture of the product;

(3) For animal drug products, determining whether the permission for commercial marketing or use of the product after the regulatory review period:

(i) Is the first permitted commercial marketing or use of the product; or

(ii) Is the first permitted commercial marketing or use of the product for administration to a food-producing animal, whichever is applicable, under the provision of law under which the regulatory review period occurred;

(4) Informing PTO whether the patent term restoration application was submitted within 60 days after the product was approved for marketing or use, or, if the product is an animal drug approved for use in a food-producing animal, verifying whether the application was filed within 60 days of the first approval for marketing or use in a food-producing animal; and

(5) Providing PTO with any other information relevant to PTO's determination of whether a patent related to a product is eligible for patent term restoration.

(b) FDA will notify PTO of its findings in writing, send a copy of this notification to the applicant, and file a copy of the notification in the docket established for the application in FDA's Dockets Management Branch (HFA-305), Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

4. Section 60.22 is amended by revising paragraph (b)(1), by redesignating existing paragraph (d) as paragraph (f), by adding new paragraphs (d) and (e), and by removing the period at the end of newly redesignated paragraph (f) and adding the following text to read as follows:

§ 60.22 Regulatory review period determinations.

* * * * *

(b) * * *

(1) The testing phase begins on the date a major health or environmental effects test is begun and ends on the date a petition relying on the test and requesting the issuance of a regulation for use of the additive under section 409 or 706 of the Act is initially submitted to FDA.

* * * * *

(d) For animal drugs:

(1) The testing phase begins on the date a major health or environmental effects test is begun or the date on which the agency acknowledges the filing of a notice of claimed investigational exemption for a new animal drug, whichever is earlier, and ends on the date a marketing application under section 512 of the Act is initially submitted to FDA.

(2) The approval phase begins on the date a marketing application under section 512 of the Act is initially submitted to FDA and ends on the date the application is approved.

(3) For purposes of this section, a "major health or environmental effects test" may be any test which:

(1) Is reasonably related to the evaluation of the product's health or environmental effects, or both;

(2) Produces data necessary for marketing approval; and

(3) Is conducted over a period of no less than 6 months duration, excluding time required to analyze or evaluated test results.

(f) * * *, or, in the case of a new animal drug in a Category II Type A medicated article, on the date of publication in the Federal Register of the notice of approval pursuant to section 512(i) of the Act. For purposes of this section, the regulatory review period for an animal drug shall mean either the regulatory review period relating to the drug's approval for use in nonfood-producing animals or the regulatory review period relating to the drug's approval for use in food-producing animals, whichever is applicable.

Dated: November 26, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

[FR Doc. 91-3429 Filed 2-12-91; 8:45 am]

BILLING CODE 4160-01-M

Exhibit 10

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 13 2004

NADA 141-186 E-0013

IDEXX Pharmaceuticals, Inc.
Attention: Randy C. Lynn, DVM, MS, DACVCP
Director of Regulatory Affairs
4249 Piedmont Parkway, Suite 105
Greensboro, North Carolina 27410

received
5-21-04

Dear Dr. Lynn:

In an original new animal drug application (NADA) dated August 26, 2003 (E0013), and amended December 2, 2003 (T0014), February 23, 2004 (T0015), February 24, 2004 (T0016), March 3, 2004 (T0017), and March 19, 2004 (T0018), you requested approval of SURPASS (1% diclofenac sodium) topical antiinflammatory cream, indicated for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal (hock, knee, fetlock, and pastern) joints in horses.

Your application is approved. A notice of this approval is being forwarded for publication in the FEDERAL REGISTER. Prior to distribution and marketing, three copies of each component of the final printed labeling must be submitted to CVM. This labeling should be identical to the facsimile labeling submitted on March 19, 2004 (T0018).

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

Manufacturing process validation is required under GMPs (21 CFR Parts 211 and 226). A product that does not conform to GMPs is adulterated (21 USC 351(a)(1)(B)). If manufacturing process validation information was not available or was found deficient at the time of the pre-approval inspection, the appropriate FDA District Office should be contacted after such validation has been completed on production lots and prior to shipment of the drug product. FDA may take regulatory action if drug products are shipped prior to completion of the validation process.

An expiration dating of 24 months is acceptable for this product.

If you submit any correspondence in the future relating to this approval, you should include a citation to this letter by date and NADA number. Any request to change the conditions of approval may require the submission of a supplemental application. If you have any questions, please contact Dr. Melanie R. Berson, Director, Division of Therapeutic Drugs for Non-Food Animals, at 301-827-7540.

Sincerely yours,

Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

Enclosure: Freedom of Information Summary

Date of Approval: MAY 13 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-186

SURPASS

(1% diclofenac sodium)

SURPASS is indicated for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal (hock, knee, fetlock, and pastern) joints in horses.

Sponsored by:
IDEXX Pharmaceuticals, Inc.

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1. GENERAL INFORMATION:

a.	File Number:	NADA 141-186
b.	Sponsor:	IDEXX Pharmaceuticals, Inc. 4249-105 Piedmont Pkwy. Greensboro, NC 27410 Drug Labeler Code: 065274
c.	Established Name:	1% diclofenac sodium
d.	Proprietary Name:	SURPASS
e.	Dosage Form:	topical cream
f.	How Supplied:	124 gram trilaminate tubes
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	1% diclofenac sodium
i.	Route of Administration:	topical
j.	Species/Class:	horse
k.	Recommended Dosage:	Wear rubber gloves to prevent absorption into the hands. Apply a five-inch (5") ribbon of cream twice daily over the affected joint for up to five days. Rub the cream thoroughly into the hair covering the joint until it disappears.
l.	Pharmacological Category:	nonsteroidal anti-inflammatory drug (NSAID)
m.	Indications:	SURPASS is indicated for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal (hock, knee, fetlock, and pastern) joints in horses.

2. *EFFECTIVENESS:*

a. Dosage Characterization:

Seventeen horses received topical diclofenac once daily for five days (18 horses received placebo). The applied dose was estimated as a three-inch ribbon of test article cream (as measured against a three inch piece of paper), and administered topically once a day to the 35 horses. Following the study, tube weights were used to determine the actual dose that each horse received. Horses received an average dose of 100 mg diclofenac once daily (doses ranged from 38 to 136 mg per day).

variable	placebo	diclofenac
lameness improved	10/18 (55%)	8/17 (47%)

The primary variable for the demonstration of effectiveness was the subjective evaluation of lameness by study investigators. After five days of treatment, lameness examinations did not show effectiveness for diclofenac; therefore, the study protocol was amended to provide twice daily administration (the dose was doubled).

The twice daily treatment portion of the study comprised the field study (see SUBSTANTIAL EVIDENCE section below), and confirmed the effectiveness of the twice daily dosage. In the field study, horses received a mean dose of 73 mg per application (the amount of diclofenac in mg that is contained in 5 inches of cream).

The twenty-eight day Target Animal Safety study evaluated SURPASS for approximately three times the labeled duration of administration (see TARGET ANIMAL SAFETY section below).

Therefore, the effective dose is 5 inches (73 mg) of 1% diclofenac topical anti-inflammatory cream, administered twice daily for up to ten days.

b. Substantial Evidence:

Title: Placebo-controlled FIELD STUDY to evaluate the safety and effectiveness of topically applied 1% diclofenac anti-inflammatory cream for the control of pain and inflammation associated with osteoarthritis (OA) in horses (BRP-DEQ-02/twice daily results).

Investigators/Study Locations:

William P. Diehl, DVM Mayo and Rofe Equine Clinic Middleburg, VA	Mike Parker, DVM Walnut Creek, CA
John M. Donecker, VMD, MS, DABVP Reidsville, NC	Bradley S. Root, DVM Albuquerque Equine Center Albuquerque, NM
Dan Flynn, VMD Georgetown Equine Hospital Charlottesville, VA	Roger Sifferman, DVM Bradford Park Veterinary Hospital Springfield, MO
Richard Henninger, DVM, MS, DACVS, DABVP University Equine Veterinary Services Findlay, OH	Barbara Lynn Smith, DVM, MS, PhD, DACVS Corvallis, OR
Jim Mitchell, DVM Cream Ridge, NJ	Nick Vatistas, BVSc, PhD, DACVS, MRCVS Vacaville, CA
Scott A. Nebergall, DVM Arthur, IL	

Animals: A total of 82 client-owned horses diagnosed with osteoarthritis (by lameness examination and radiography) were included in the final analysis of the field study. Horses (51 geldings, 28 mares and 3 stallions), ranging in age from 2 to 30 years, were treated with test cream. Forty-two horses were treated twice daily with 1% diclofenac topical anti-inflammatory cream; forty horses received placebo cream.

Descriptions of osteoarthritic conditions in the 82 horses are listed in the following table:

Descriptions of Osteoarthritic Horses

		Placebo (n=40)	Diclofenac (n=42)
Study Joint	Carpus (knee)	5	8
	Tarsus (hock)	16	18
	Stifle	0	1
	Pastern	5	8
	Fetlock	14	7
Study Leg	Left Side	26	19
	Right Side	14	23
	Forelimb	22	22
	Hindlimb	18	20
Disease Duration	Chronic (>1 month)	37	37
	Acute (<1 month)	3	4
	Unknown	0	1
Mean Duration	Months (min-max)	25.0 (0.5-120)	21.1 (0.13-120)
Disease Severity	Mild	16	20
	Moderate	14	12
	Severe	10	10

Treatment Groups: Horses received either diclofenac 1% cream or placebo cream, rubbed into the hair on the affected joints until the cream disappeared.

Dosage: Horses received a mean dose of 73 mg of diclofenac (ranging from 27 to 111 mg per application), twice daily. Actual dose received was determined by tube weight measurements for each horse, and is equivalent to the application of a five-inch ribbon of cream.

Route of Administration: topical

Frequency and Duration of Treatment: twice daily for five days

Variables Measured:

Investigators examined the horses on days 1 (baseline), 2, 3, 4 and 5 and recorded lameness, pain and mobility scores. The scores were evaluated statistically. The horse owner also evaluated the horse daily for lameness each day. The investigator applied at least one of the two daily treatments. Blood samples were collected for hematology and serum chemistry on days 0 and 5.

The primary variable for success was lameness examination by the veterinarian. Criteria for success for each variable was met when improvement by at least one score point was noted. Scores for each variable were assigned as follows:

Lameness (primary variable):

0 = lameness not perceptible under any circumstances
1 = lameness is difficult to observe and not consistently apparent, regardless of circumstances (for example, weight carrying, circling, inclines, hard surfaces, etc.)
2 = lameness is difficult to observe at a walk or when trotting in a straight line, but is consistently apparent under certain circumstances (for example, weight carrying, circling, jogging on inclined or hard surfaces)
3 = lameness is consistently observable at a trot under all circumstances
4 = lameness is obvious at a walk
5 = lameness produces minimal weight bearing in motion and/or at rest or a complete inability to move

Joint pain:

The joint was manipulated through a normal range of motion and subjectively scored:

0 = no pain
1 = mild pain (horse calmly withdraws limb)
2 = moderate pain (horse withdraws limb and exhibits some signs of distress)
3 = severe pain (horse withdraws limb and exhibits severe distress)

Joint mobility:

The joint was manipulated through a normal range of motion and subjectively scored in comparison to Day 0:

0 = no change from Day 0
1 = 5-10% improvement from Day 0
2 = 11-20% improvement from Day 0
3 = >20% improvement from Day 0

Evaluation by horse owner in comparison to Day 0:

0 = worse
1 = no change from Day 0
2 = slight improvement from Day 0
3 = much improvement from Day 0
4 = normal (no signs of pain, stiffness or lameness)

Statistical Methods: The percentage of horses that improved in each group was evaluated with an exact test of the common odds ratio, stratified by investigator, with a two-tailed α of 0.05.

Results: The percentage of horses treated with twice daily diclofenac that showed improvement in lameness score was significantly greater than the percentage of horses in the placebo group (p=0.0059). Seventy-four percent of horses treated with twice daily diclofenac showed improvement in lameness, while 40% of horses treated with placebo showed improvement.

Variable	**Placebo**	**Diclofenac**	**p-value**
	Number of horses showing improvement by at least one grade / Total number of evaluable horses		
Lameness Improved	16/40 (40%)	31/42 (74%)	p = 0.0059
Pain Improved	15/40 (38%)	20/42 (48%)	p = 0.4507
Mobility Improved	9/40 (23%)	12/42 (29%)	p = 0.3887
Improvement Noted by Owner	20/40 (50%)	30/41 (73%)	p = 0.0950

Bloodwork: Day 5 blood samples for one investigator (19 horses) were not immediately analyzed, resulting in artifacts in the results for glucose, phosphorus, potassium, hemoglobin, hematocrit, and red blood cell levels. Therefore, post-treatment results were not available for 19 horses for these bloodwork parameters.

During the study, no clinically relevant abnormalities were identified from hematology or serum chemistry samples (comparing baseline to day 5), except for one horse that colicked (see adverse reactions). Day 5 bloodwork for this horse showed decreases in RBC, Hb, and HCT, with an increase in PMNs (compared to pretreatment values):

blood parameter	pretreatment (day 1)	day 5	laboratory reference values
HCT (%)	45.9	27.1	37-55
RBC (x $10^6/\mu l$)	8.35	5.13	4.5-7.5
Hb (g/dl)	16.1	9.6	12-18
PMNs (x $10^3/\mu l$)	50	78	50-77

Adverse Reactions: One diclofenac-treated horse developed colic and responded to symptomatic treatment on day four of the study. One horse treated with placebo exhibited mildly jaundiced mucous membranes on day five; bloodwork for this horse was unremarkable. No other adverse reactions were noted during the study.

Conclusions: The study demonstrated an improvement in clinical lameness associated with OA in horses when diclofenac was administered twice a day. Adverse reactions were not definitively attributed to the use of diclofenac 1% cream.

3. *TARGET ANIMAL SAFETY:*

Title: Target Animal Safety Study of 1% diclofenac sodium topical anti-inflammatory cream applied topically to horses (study # 98308h, BRP-DEQ-06)

Purpose: To evaluate the safety in horses of three dosage levels (0.6X, 1.7X, and 2.8X) of 1% diclofenac sodium topical anti-inflammatory cream in a 28 day study. An additional group received 5.6X the recommended dose, given on a single day, and followed by a 14 day observation period.

Investigator: John W. Campbell, Ph.D.

Study Location: Southwest Bio-Labs, Inc.
Las Cruces, NM

Animals: Thirty horses (15 geldings and 15 mares), approximately 3 to 18 years old, six horses per group (3 geldings and 3 mares).

Dosage Groups:

treatment group	no. of horses	diclofenac daily dose (mg*)	no. of diclofenac-treated joints/day
1	6	0 (0X)	0 (sham-dosed)
2	6	82 (0.6X)	1
3	6	246 (1.7X)	3
4	6	410 (2.8X)	5
5	6	820 (5.6X)	10 (5 joints treated twice on a single day)

*Based on tube weight measurements per group, the average dose per application contained 41 mg diclofenac.

Route of Administration: Topical

Frequency of Treatment:

Groups 1-4: Treated every day for 28 consecutive days
Group 5: Treated for a single day, followed by a 14 day untreated observation period.

Duration of Study: 28 days for groups 1-4; 14 days for group 5.

Variables measured:

Groups 1 through 4:

-Clinical examinations were conducted on days 5, 12 and 19, and a complete physical examination was conducted prior to treatment and at termination.
-Horses were observed once daily for clinical abnormalities.
-Body weights were recorded on days -8, -1, 5, 12, 19 and prior to termination.
-Hematology and serum chemistry samples were drawn on days -3, 6, 13, 20 and 27 or 28 (Note: GGT, fibrinogen, and bleeding times were not evaluated during the study).
-Urinalyses (midstream) were performed on days -2 or -1 and 27 or 28.
-Feces were evaluated (blood, color, consistency, parasites, other abnormalities) on days -2 or -1 and 28.
-Synovial fluid was withdrawn from one joint prior to treatment. During necropsy, each horse had one treated and one contralateral untreated joint sampled.
-Necropsy: Gross pathology and histopathology were evaluated in all horses. Limited histopathology results were obtained from horses in groups 2 and 3 (dermal tissue, liver, stomach, all sections of the intestinal tract, treated and untreated joints, and uterus).

Group 5:

Variables for the 5.6X group were the same. Results for this group were compared to placebo results.

-Clinical examinations were conducted on day 4, and a complete physical examination was conducted prior to treatment and at termination.
-Horses were observed once daily for clinical abnormalities.
-Body weights were recorded prior to the study, days 4 and 13.
-Hematology and serum chemistry samples were drawn prior to study, day 5 and 12 (Note: GGT, fibrinogen, and bleeding times were not evaluated during the study).
-Urinalyses (midstream) were performed prior to study and day 12 or 13.
-Feces were evaluated (blood, color, consistency, parasites, other abnormalities) prior to study and day 13.
-Synovial fluid was withdrawn from one joint prior to treatment. During necropsy, each horse had one treated and one untreated joint sampled.
-Necropsy: Gross pathology and histopathology were evaluated in all horses.

Results:

Weight loss: One horse in the 2.8X treatment group had increased GI sounds prior to treatment and broke with diarrhea during the study, losing a total of 20 kg (the most weight lost by any horse in groups 1 through 4). Necropsy of the GI tract of this horse was normal; no signs of GI parasitism were noted.

Horses in the 5.6X treatment group (single administration) lost more weight per horse over 14 days compared to the other 4 treatment groups. Four of six horses in the 5.6X group lost weight during the 14 day study (between 13 and 29 kg). One of these horses exhibited signs of upper respiratory illness prior to treatment (cough, nasal discharge, elevated WBC count), and showed clinical improvement during the study. Evidence of strongyle parasitism was also noted at termination in this horse. The other three horses in this group that lost weight did not show other clinical signs or evidence of inappetence.

Gastric ulcer: Gross necropsy of one horse in the 5.6X group showed a thickened stomach wall and an ulcer (1x3 cm) in the glandular portion of the stomach. Histologically, the ulcerated area showed chronic mild inflammation, mild fibrosis and fibroplasia. Other clinical signs associated with NSAID toxicity (colonic ulceration, hypoproteinemia, hypoalbuminemia) were not noted in this horse.

Joint fluid: The synovial fluid of one horse in the 2.8X dosage group contained elevated WBCs at termination, possibly the result of pretreatment removal of joint fluid. This horse did not show other abnormal clinical signs.

Plasma concentrations of diclofenac following topical administration: Dose dependent increases in blood levels of diclofenac were detected in horses at 1.7X (three of six horses) and 2.8X (six of six horses) the recommended dose.

Conclusions:

The correlation of clinical pathology results with clinical observations and necropsy results did not reveal any individual horses showing definitive signs of NSAID toxicity. It should be noted that clinical pathology results did not include an evaluation of GGT, fibrinogen, or bleeding times.

Clinical signs of illness during the study that may have been related to the administration of diclofenac were weight loss in 4 (of 6) horses in the 5.6X group, and possible exacerbation of existing gastrointestinal (GI) disturbances in one horse in the 2.8X group. The etiology of the glandular gastric ulcer in the 5.6X group remains unknown.

4. *HUMAN SAFETY:*

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows:

> Not for use in horses intended for human consumption.
>
> *User Safety:* Keep out of reach of children. Not for human use. Consult a physician in case of accidental ingestion by humans. Wear gloves to prevent absorption into the hands. Direct contact with the skin should be avoided. If contact occurs, the skin should be washed immediately with soap and water.

5. *AGENCY CONCLUSIONS:*

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that SURPASS when used under the labeled conditions of use is safe and effective for the control of pain and inflammation associated with osteoarthritis (OA) in tarsal, carpal, metacarpophalangeal, metatarsophalangeal and proximal interphalangeal (hock, knee, fetlock and pastern) joints in horses.

The drug is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is required to diagnose equine osteoarthritis and to monitor response to treatment.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

SURPASS (1% diclofenac sodium) Topical Anti-Inflammatory Cream is under the following U.S. patent numbers:

US 4,761,288 expires August, 2, 2005
US 4,897,269 expires January, 30, 2007
US 4,937,078 expires June, 26, 2007

6. ***ATTACHMENTS:***

Facsimile labeling is attached as indicated below:

a. Package Insert
b. Client Information Sheet
c. Tube Label
d. Box Label
e. Display Box Label

Exhibit 11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,937,078		)
		)
Granted:	June 26, 1990	)
		)
Patentees:	Michael MEZEI and Adrienn GESZTES	)
		)
		)
Assignee:	Mezei Associates Limited	)
		)
FOR:	LIPOSOMAL LOCAL ANESTHETIC AND ANALGESIC PRODUCTS	)

Commissioner for Patents
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Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

LETTER AUTHORIZING MEZEI ASSOCIATES, LTD. TO RELY ON ACTIVATES OF BLUE RIDGE PHARMACEUTICALS INC. FOR THE PURPOSES OF OBTAINING A PATENT TERM EXTENSION

For the purposes of obtaining a patent term extension of the above-identified patent under 35 U.S.C. § 156, Mezei Associates, Ltd. ("Mezei") is authorized to rely on activities undertaken by Blue Ridge Pharmaceuticals Inc. ("Blue Ridge, " now IDEXX Pharmaceuticals, Inc. ("IDEXX")) before the United States Food and Drug Administration ("FDA") for obtaining marketing approval for SURPASS®

Date: 7/2/04

Neil Y. Gilbert
Patent Counsel
IDEXX Pharmaceuticals. Inc.
One IDEXX Drive
Westbrrok, ME 04092